ANNALS OF
INTERNAL MEDICINE

VOLUME 8 OCTOBER, 1934 NUMBER 4

THE MONOCYTE, MONOCYTOSIS, AND MONOCYTIC LEUKOSIS: A CLINICAL AND PATHOLOGICAL STUDY *

By CHARLES A. DOAN, M.D., F.A.C.P., and B. K. WISEMAN, M.D.,
Columbus, Ohio

THE MONOCYTE AND THE CELLS OF THE BLOOD
THE MONOCYTE AND THE CELLS OF THE CONNECTIVE TISSUES
THE MONOCYTE IN PATHOLOGIC STATES
THE MONOCYTE IN LEUKEMIA
CHRONIC MONOCYTIC LEUKEMIA
MONOCYTIC LEUKEMIA WITH ALEUKEMIC PHASE; LEUKEMIA CUTIS
ACUTE MONOCYTIC LEUKEMIA
THE PROBLEM OF MIXED LEUKEMIA
ETIOLOGIC CONSIDERATIONS
DISCUSSION
SUMMARY

MODERN cytologic, physiologic and pathologic studies have left little doubt as to the separate identity and functional independence of the monocyte of the blood and connective tissues. Adequate criteria in fixed as well as supravital technics are now available for sharply differentiating this strain of cells from the other leukocytic elements in the circulating blood, and important new diagnostic and prognostic interpretations of great significance are attaching to the data rapidly accumulating from the newer blood studies in such conditions as tuberculosis,[1-6] pneumonia,[7] Hodgkin's disease [8] and syphilis,[9] to mention only the more outstanding examples.

THE MONOCYTE AND THE CELLS OF THE BLOOD

The history of the changing conceptions, which have from time to time been held concerning the monocyte, follows closely the development of new technics, each bringing its additional clarifying criteria of physiologic or morphologic significance to the problem. The monocyte was first considered in the original Ehrlich classification as a transitional form in the maturation of the neutrophilic leukocyte. Naegeli concurred in this view. With the introduction of the Romanowsky methylene blue-azur staining

* Read in part before the American College of Physicians, Chicago, Ill., April 17, 1934.
From the Department of Medical and Surgical Research, Ohio State University.

technic, Michaelis and Wolfe [10] (1902) observed that monocyte and lymphocyte both contained azur granules, the neutrophiles having quite different specific granular bodies; and Pappenheim and Ferrata [11] conclusively demonstrated in 1911 the independence of blood monocyte and granulocyte. The fact that monocytes are found only under pathologic conditions in the bone marrow [12] but may be found regularly arising in the spleen [13] and peripheral lymph nodes,[14] further tended to link monocyte and lymphocyte, and the evidence of tissue culture [15] has been interpreted in support of a genetic relationship between these two cell strains. The azur granules, however, of the lymphocyte are relatively large, few in number, and inconstant in a clear cytoplasm, while the azurophilic granules of the human monocyte are tiny, usually extremely numerous, and imbedded in a dense, opaque, moderately deeply basophilic background. Schilling-Torgau,[16] carefully analyzing these differential morphologic criteria, in 1912 definitely described the monocyte as making a third strain of the white cells, distinct on the one hand from lymphocytes and on the other from granulocytes, and thereby became the first hematologist prepared to recognize any dyscrasia specifically involving the monocyte. It is not surprising, therefore, that the very next year, 1913, Schilling-Torgau with Reschad [17] should have discovered and reported the first case of monocytic leukemia. The more recent studies of the monocyte by Sabin and her coworkers [2] and of the lymphocyte by Wiseman [18] have produced a new wealth of evidence substantiating the independence of each of these cell strains and their frequent reciprocal relationship to each other in various pathologic states.

The Monocyte and the Cells of the Connective Tissues

There still exists, however, a widespread skepticism as to the existence of a leukemic state involving primarily and solely this so-called monocyte of the blood and its anlagen in the connective tissues. This is explainable perhaps upon two grounds: first, a continuing inability on the part of the average physician and laboratory technician to identify and sharply differentiate in ordinary blood films this distinctive cell type; and second, a confusion relative to nomenclature, functional specificity, and morphologic differentiation of the cells of the connective tissues which is quite as profound and widespread as that involving the cells of the blood. Ranvier [19] in 1891 described the powers of phagocytosis exhibited by certain free connective tissue cells which he termed "clasmatocytes." Metchnikoff [20] (1883–1892) then differentiated the circulating ameboid phagocytic polymorphonuclear cells of the blood, "microphages," from the relatively less ameboid phagocytic "macrophages" of the tissues, including among the latter the stellate cells of Kupffer in the liver, certain endothelial cells and the large mononuclear cells of the tissues, splenic pulp and lymph nodes. Marchand [21] demonstrated the derivation of clasmatocytes from mesenchymal elements more especially those found in the adventitial sheath of

blood vessels, and showed that in inflammation these adventitial cells were transformed into the macrophages of Metchnikoff. Maximaw [22] (1902) also studied the mononuclear ameboid phagocytes in inflammatory tissues calling them "polyblasts." Ribbert [23] (1904) then found that cells of this group picked up colloidal suspensions of various composition, as for example sugar of iron, and that they segregated non-toxic dyes such as lithium carmine when the latter were introduced into the blood stream. This intravitam reaction was quite specific in that general vascular endothelium and fibroblasts took a negligible part in the phagocytic phenomenon, and muscle fibers rejected these vital dyes entirely. Goldmann [24] and his associates followed with a study of the cells reacting to pyrrhol blue, demonstrating the identity of Ranvier's clasmatocytes with Marchand's adventitial cells and Maximaw's polyblasts. In 1913 Aschoff and Kiyono [25] introduced the term "histiocyte" to designate this mesenchymal mononuclear phagocyte of the connective tissues and popularized the reticulo-endothelial concept based upon the observed degree of intensity and frequency of phagocytosis by this specific group of cells in the connective tissues.

This was the general situation when interest became aroused in a new range of criteria for differentiating the mononuclear cells of the blood afforded by the application of neutral red and Janus green to living cells through a supravital technic. While practically the whole experience with tissue culture [26, 27] up to the present time has tended to strengthen the position that monocyte of blood and clasmatocyte of tissue are but different phases in the life cycle of one strain of cells,—the connective tissue macrophage,—both supravital-morphologic and clinical-pathologic studies have been accumulating which provide pertinent data raising at least a reasonable doubt as to the validity of this conclusion. When the living cells are studied supravitally, the monocyte, whether in the blood or in the tissues, reacts to the neutral red with a rosette of small vacuoles staining a characteristic uniform salmon pink and arranged more or less symmetrically in a concentric halo about the centrosphere in the hof of the nucleus. Dark field examination of fresh unstained blood films confirms this pattern as indigenous to the normal living cells and not an artefact or the result of a toxic reaction to the dyes. Neither lymphocyte, granulocyte nor clasmatocyte contains such a pattern of vacuoles, either in the presence or absence of the dyes mentioned, and the pH of the intravacuolar fluid in the monocyte as revealed by the indicator neutral red (pH 6.8–8.0) is so constant as to give a uniform tinctorial reaction which characterizes the monocyte throughout the animal kingdom. These structures so readily demonstrated in the living monocyte are not identical with the azurophilic granules revealed in the fixed films stained with the Romanowsky dyes. Furthermore, a careful quantitative survey of peroxidase stained films usually rewards the discriminating searcher with definite differences in the degree and distribution of oxidase granules in the monocytes as contrasted with granulocytes,[28] the

lymphocytes always, of course, being oxidase negative. The first specific vacuoles appear, as do the granules of the myelocyte, in a primitive basophilic cell, the *monoblast,* which passes through a developmental period consisting in the gradual elaboration of these structures before functional maturity and motility appear.[29] Unlike the definitive granulocytes and erythrocytes, the monocyte of the circulation continues to show numerous mitochondria and retains the power of mitosis, division figures being encountered not infrequently in the blood stream under relatively normal conditions. The clasmatocyte, in contradistinction, is seldom seen in the peripheral circulation in health.[30] It is usually a larger cell without apparent maturation cycle, with no cytoplasmic pattern, more highly phagocytic than the monocyte for larger bodies, such as whole red and white cells, and with segregation vacuoles reacting to neutral red in a range from yellow to deep maroon, i.e., over the entire pH indicator range of neutral red. In brief, the supravital studies of Sabin, Doan and Cunningham [2, 31] have resulted in data which help to clarify the issues thus far discussed in three directions: (1) the rosette of vacuoles reacting to neutral red in the living monocyte, when taken in combination with other distinctive morphologic criteria, sharply differentiates this cell from each of the other types of blood and tissue cells, thus supporting and confirming the previous evidence upon which its separate identity has rested; (2) the monocyte of the blood is identical with the monocyte of the tissues and reflects directly and quantitatively the proliferative activity of these elements in the body as a whole; (3) the mononuclear phagocytes of the tissues making up the so-called reticuloendothelial system, are of two morphologic, functional and probably genetically distinct strains, the one (the monocyte) a derivative of mesenchymal reticular tissue, the other (the clasmatocyte) an endothelial derivative, of Kupffer cell and splenic macrophage type. While no unanimity of opinion as to its exact life history has as yet been reached, as was emphasized recently by Forkner,[32] who listed no less than 19 separate views as to the origin of the monocyte, it is our belief that the clinico-pathologic evidence beginning to accumulate upon the basis of the now adequate morphologic criteria essential to the recognition and differentiation of this cell, already bids fair to confirm more conclusively a mesenchymal connective tissue anlagen for the monocyte identical with or closely similar to that from which the lymphoblast and myeloblast arise. The balance of specific differentiating stimuli at any given time or location must determine the character of the definitive cell type to be produced.

Thus, the monocyte, threatened repeatedly with incorporation into the life cycle of one or other of the firmly established strains of the white cells, and surviving this fate only to have its birthright threatened once again in the discussion as to the oneness of all mononuclear phagocytes in the tissues, has survived successfully nevertheless, these histological and physiological controversies of recent years.

The Monocyte in Pathologic States

Perhaps the most extensive and complete studies of the monocyte in disease have been those initiated by Sabin and her associates [1, 2] in the analysis of the cellular reactions in tuberculosis. The epithelioid cell of the tubercle has been proved to be but an altered phase in the life cycle of the monocyte. Except in caseous foci the tubercle bacilli are found almost exclusively within the epithelioid cells, apparently in symbiotic interrelationship,—a manifestation of the phagocytic receptiveness of this mononuclear cell. In experimental tuberculous disease, prior to the appearance of any increase in mature monocytes in the blood or of epithelioid cells in the tissues, a marked hyperplasia of primitive blast cells occurs at the point of lodgment of acid fast organisms.[29] These have been proved to be monoblasts by the subsequent observance of their speedy maturation into typical monocytes and epithelioid cells within which the tubercle bacilli are thereafter usually found. Coincident with, and not prior to, the increase of these cells in organs and tissues there appears an increase in their representation in the circulating blood. Consequently, an absolute monocytosis in the blood in tuberculosis indicates the progressive formation of new tubercles in the tissues. When taken in conjunction with the qualitative as well as the quantitative data now determinable for granulocytes [33, 34] and lymphocytes [18, 35] a valuable source of information about any given tuberculous patient is at once available.

The biological studies, however, of the chemical fractions from the acid fast bacteria have laid the foundation for the most promising conception of the nature of the fundamental stimuli responsible for monocytic proliferation. A thorough survey extending through the past decade with adequately prepared and controlled chemical fractions [36] has established conclusively the fact that the lipoids, more particularly the tuberculo-phosphatides, are solely responsible for the monocyte-epithelioid proliferation and differentiation in tuberculosis, and that the ultimate active principle is to be found in one or more of the newly isolated fatty acids from this material.[2]

It is of interest in this connection to note that a similar response to lipoids has not been observed for the clasmatocytic elements of the connective tissues. In experimental kala azar,[37] however, there appears to be as specific host-parasite relationship between clasmatocyte and the *Leishmania donovani* bodies as in tuberculosis between monocyte and tubercle bacilli. A sharper pathologic differentiation of these two cell types is thus exemplified in the tissue reactions of these two diseases than exists physiologically, which suggests different inherent cell-strain capacities for phagocytic response.

Other conspicuous examples of the monocytic reaction to bacterial invasion are provided in syphilis,[9] typhoid fever,[38] undulant fever,[39] and in *B. monocytogenes* infection of rabbits.[40] In lobar pneumonia, Hickling [7]

has demonstrated a transitory reflection in the blood of an increased mobilization of monocytes in the lung during the period of resolution, the monocytosis being indefinitely maintained if empyemic complications arise. Under these circumstances the demand for an increased phagocytic function is apparent and prognostic data are accordingly enhanced when the monocyte factor is recognized.

The Monocyte in Leukemia

During the latter part of the last century it was currently believed that all acute leukemias were of lymphoid origin. Fraenkel [41] in 1895, among others, emphasized the lack of differentiating criteria, which marked the cells of the majority of such syndromes as lymphocytic elements. With the recognition and separation of the myeloblast on morphologic grounds by Naegeli [42] in 1900, it became gradually apparent that many of the cases which upon superficial examination revealed a predominance of cells without the usual complement of specific granules in the cytoplasm, nevertheless represented disturbances in myelopoiesis so profound as to permit the delivery into the active circulation of greater or lesser numbers of these agranular, myeloblastic elements, usually restricted to the marrow.[43, 44, 45] The elaboration of new technics for the accentuation of the differences, which become less and less distinctive and characteristic of the respective cell strains the earlier the individual units are seen in their respective maturation cycles, has made for continued progress in the differential diagnosis of this group of leukemic dyscrasias. Schilling's comparable contribution (1912) toward the separate identity of the monocyte, laid the foundation for the recognition of the third type of leukemia, but despite Schilling's pioneer observations made more than two decades ago, a leukemia in which the monocyte seems to be primarily involved is only just beginning to be recognized sufficiently widely and frequently to furnish the basis for clinicopathologic studies leading toward the revelation of further details about this strain of cells. As may be seen from the accompanying diagram, the monocyte satisfies all of the theoretic demands necessary for the development and appearance of pathologic states parallel to and characterized by the same varying symptomatology as those involving the longer established cell strains. If the medical literature on this subject may be subjected to interpretation at all, it reveals the protean manifestation of clinical signs and symptoms which has obtained in the cases reported as suffering from monocytic leukemia. A personal experience during the past four years with some 75 cases of leukemia (table 1) of all types and degrees of severity

Table I

The Leukemias of All Types Studied during a Four Year Period

Total Cases 1930–34	76
Myeloid Leukemia	28–37%
Lymphatic Leukemia	36–47%
Monocytic Leukemia	12–16%

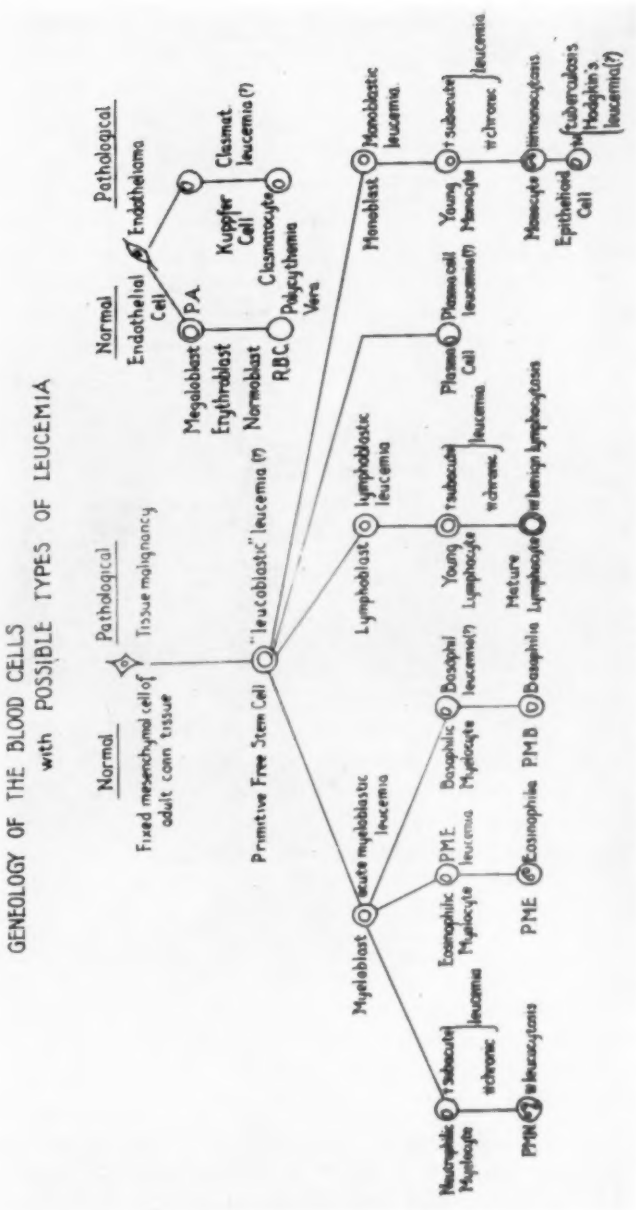


DIAGRAM 1. The relationship of the normal maturation stages in the blood cells to pathologic conditions more or less specific for the cell type and age indicated. A parenthetic question mark (?) is placed after those pathologic conditions which theoretically should occur but which still remain to be identified satisfactorily. Polycythemia vera may be said at the present time to bear something of the same pathologic relationship to the erythrocyte that leukemia does to the white cells, the latter being involved also in this disease in a pan-marrow hyperplasia.

and manifesting widely divergent cellular reactions has made the present authors keenly aware that the only basis upon which ultimate differentiation of the several types can be accurately and consistently made is that which rests upon the morphologic and behavior characteristics of the circulating cells themselves as they appear under the conditions provided by supravital as well as fixed staining technics. There is no clinical syndrome in our experience which is pathognomonic of monocytic leukemia as distinct from myeloid or lymphatic leukemia. Certain generalizations have been attempted by some authors but these have been made largely from analyses of the literature since no single investigator has as yet had a personal experience great enough to draw upon statistically; and it is our opinion that up to the present moment the difficulties inherent in the differentiation and identification of lymphoblast, myeloblast and monoblast, to say nothing of more mature monocytes and myelocytes " B," have been sufficiently great to render it worse than useless to attempt to judge from " the published records " the principle underlying cellular pathology in any given case. And this is not to doubt the authenticity and existence of many more cases of monocytic leukemia than have begun to be reported. Dameshek,[46] reviewing the literature up to and including 1929, was inclined to accept 18 of the 31 then reported cases. Clough [47] in a further analysis (1932) endorsed as true instances of monocytic leukemia 22 of the then accrued 39 cases. Up to and including the early part of this year, 1934, we have found some 75 reported cases exclusive of those designated as aleukemic reticulo-endotheliosis, many of the latter doubtless belonging in this general group. Because of the reasons cited, we prefer not to attempt a critical evaluation of the individual cases. Ultimately the registry for thoroughly studied and authenticated cases of monocytic leukemia which the Clinical Pathologists have organized under Dr. Kracke's direction, will furnish the proper basis for such an appraisal and statistical analysis.

Our own experience confirms the general impression conveyed by the literature that every feature common to myeloid and lymphatic leukemia has been found in the monocytic form. Thus, monocytic leukemia has been reported as occurring at any age from 11 months [48] to 71 years [49]; and it may be relatively chronic,[50, 51, 52] subacute [53–56] or fulminant [32, 50, 57–59, 64, 69] or it may, with leukemic or aleukemic blood, present a confusing picture of the so-called mixed leukemia type; it may be associated with a neoplastic growth [48] similar in all respects to leukosarcoma [62]; it has shown the skin manifestations of leukemia cutis.[65, 68] Cases without demonstrable splenomegaly,[47, 49, 57, 59] lymphadenopathy [47, 56, 64] or without hemorrhagic manifestations are described.[52, 57, 66] One or other of these variations has been reported from single case studies by individual investigators usually, but it has been possible for us to observe all of these respective clinical manifestations in the present series of nine personally studied and verified cases of the disease, and to make the diagnosis in three other patients from whom blood films have been available for confirmation of the cell type involved.

During the same period we have seen from the same general cross section of patients 28 myeloid and 36 lymphatic leukemias. Our experience would thus suggest an incidence of monocytic leukemia of 16 per cent or less, with approximately 37 per cent myeloid and 47 per cent lymphoid leukemias on the basis of 76 cases studied over a four year period. The age incidence in our series has been from four to 70 years; seven were male, five female patients; the known duration of the disease was from six weeks to four years.

Chronic Monocytic Leukemia

The verification of the existence of a relatively benign, chronic state of monocytic leukosis is essential to the full establishment of this leukocytic element on a pathologic par with granulocyte and lymphocyte. A true chronicity, however, has seldom been encountered or recognized in the leukemias of monocytic type, as judged by a survey of the literature to date, though a chronic or subacute syndrome is perhaps more commonly seen than the very acute process in the leukemias of myeloid and lymphatic origin. It happens that the first case recognized by us as coming under the general category of monocytic leukemia was encountered within the first two months of the establishment of our blood clinic at Ohio State University in the fall of 1930, and represented an extremely chronic, non-progressive syndrome, the patient eventually succumbing to cerebral hemorrhage after a year's observations without an acute exacerbation of the leukemic process at any time.

Case I

J. G., white, male, aged 66 years, a retired hardware salesman, was first seen September 12, 1930, at the request of Dr. L. H. vanBuskirk. Following the extraction of 12 upper teeth January 28, 1930, there had been profuse hemorrhage persisting for 24 hours to the point of serious exsanguination, the patient fainting upon the least exertion. For several months thereafter he remained excessively weak and finally returned to his physician early in September saying he had been unable to regain his accustomed vigor since the experience of the preceding January. About 15 pounds in weight had been lost. A moderate hypertension (162/100) existed. The remaining teeth showed extensive caries. Heart and lungs were reported as essentially negative. The urine showed a trace of albumin and a few casts, no pus. The blood examination showed: erythrocytes 3,690,000, hemoglobin 60 per cent, leukocytes 12,480; and the differential count revealed PMN 33 per cent, PME 3 per cent, myelocytes 7 per cent, lymphocytes 21 per cent, monocytes 36 per cent. An elimination of obvious toxic foci in the mouth was advised and the remaining teeth were promptly extracted. No immediate difficulty ensued but one week following the extractions a severe hemorrhage occurred from the tooth sockets persisting for 24 hours and requiring the services of a physician to control. It was at this point that consultation was requested and we had the opportunity of following personally the subsequent course of events. Our first complete studies October 16, 1930, revealed 4,250,000 red cells with hemoglobin of only 6.7 gm. in 100 c.c. blood, 60,000 platelets and 26,900 leukocytes with the following supravital differential: active PMN 16.5 per cent, round 2 per cent, vacuolated 0.5 per cent, non-motile 1 per cent, baso-

philes 0.5 per cent, eosinophiles 1 per cent, myelocytes "C" 1.5 per cent, small lymphocytes 10 per cent, intermediate 1 per cent, large lymphocytes 0, monocytes, active 65 per cent, clasmatocytes 0.5 per cent, unclassified 0.5 per cent; hematocrit 31.5, average diameter erythrocytes 7.64 microns, sedimentation 25 mm. in 1 hour, icterus index 9, erythrocyte fragility 0.520–0.340.

On October 20, 1930 the patient was admitted to the Research Service, University Hospital, for a five day period of observation. Except for the dental condition and a moderate hypertension the patient had been in good general health prior to January 1930. In early childhood he was subject to chills and fever, presumably malaria for they were controlled with quinine. At 11 years and again at 20 he had pneumonia with, in each instance, a prolonged convalescence of 10 to 12 weeks. During seven years, between the ages of 54 and 61, recurrent attacks of jaundice associated with pain in the region of the gall-bladder were experienced. Other than on the two occasions previously mentioned no history of hemorrhages, epistaxis, or purpura was obtainable. The family history was entirely negative in so far as it might relate to the patient's present illness.

Physical examination on first admission to Hospital: T. 98° F., P. 70, R. 18. Blood-pressure, 170 systolic and 100 diastolic. Weight 138 pounds. There was a marked pallor. Nodes in the anterior cervical chain of the right side, 1 cm. in diameter, were palpable with none demonstrable on the left. The posterior cervical, submaxillary, submental and epitrochlear nodes were not palpable. In the left axilla two to three small nodes 1 cm. in diameter were felt but none were found on the right. A few small inguinal nodes were present. The palpable nodes were discrete, movable, elastic, not tender. The chest was negative except for a moderate degree of cardiac enlargement. The liver could be felt 4 cm. below the right costal margin; the spleen was not palpable. Reflexes not remarkable.

Laboratory Studies: The cytological studies of the blood may be followed on chart 1. Gall-bladder visualization was successful; no evidence of calculi was found and there was rapid emptying following the fat meal. The humerus, radius, femur and tibia on the right side showed no radiologic evidence of any pathologic process; a marked density of the bones of the skull was apparent. Blood chemistry: NPN 28; urea nitrogen 11.4; urea clearance 46.2. Blood culture, negative. The basal metabolic rate was plus five and plus ten on two days. Tuberculin Mantoux tests (human, bovine and avian) were all negative. Urinalyses showed granular casts (two plus), and albumin 25 mg. Phosphatid precipitin test, antigen A–3 H–37, positive 1–1280. An exploratory biopsy failed to yield the desired lymphatic tissue for histologic study.

In brief, the hospital study failed to reveal any apparent cause for the abnormal differential blood count, but confirmed beyond any reasonable doubt the monocytic character of the established mononuclear predominance in the circulation of this patient. A three hour study with observations taken at 15 minute intervals in order to appraise the rhythmic cycle of the different cellular elements showed a disordered mechanism for the monocytes, which together with the shift to the left with a dominance of quite young forms among this group, served to establish the diagnosis of chronic monocytic leukemia. The relative but not absolute decrease in granulocytes and lymphocytes with their more moderate "shift to the left" and relatively unaffected normal rhythm suggests a secondary rather than a primary participation of these elements in the syndrome.

Little change was noted during the succeeding months except that the hemoglobin increased to 12 gm. per 100 c.c. of blood by January 1931 and the platelets increased to between 130,000 and 350,000 with no hemorrhagic tendencies manifest. Desired activities were not denied the patient, and he enjoyed a relatively normal life. The total white count ranged between 15,000 and 30,000, with the monocytes representing from 11,000 to 22,000 cells.

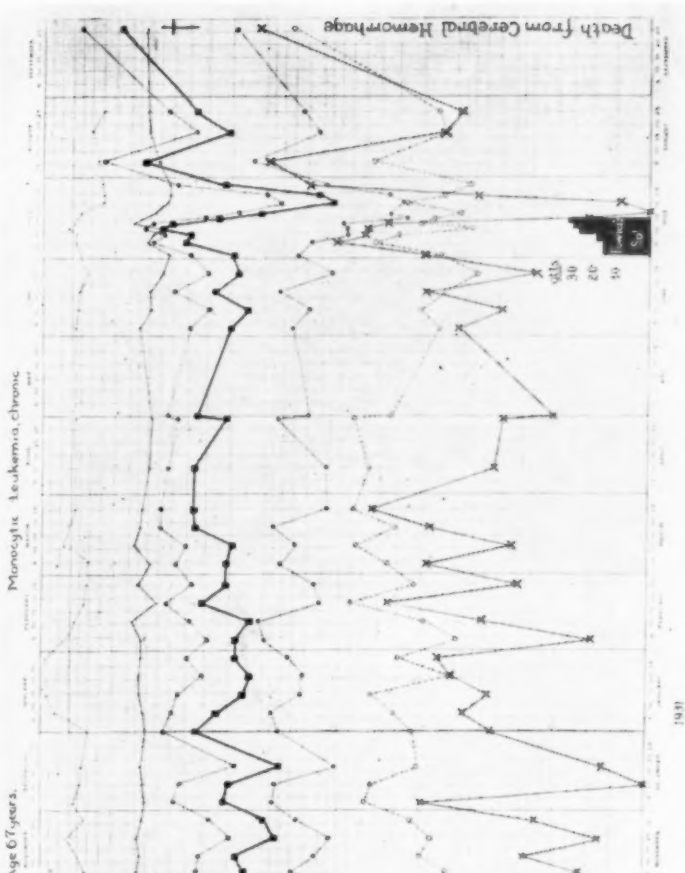


CHART 1. This patient showed a persistent monocytic elevation largely responsible for the increase in total leukocyte count, but without significant clinical symptoms of leukemia, during the year of observation. The lymphocytes were unchanged either in quality or quantity. Myelocytes were consistently present, fluctuating between 200 and 2,000 per cu. mm. During the period of arsenic medication the myelocytes were reduced as well as the mature granulocytes, but on the rebound following the stopping of the medicine they rose to a high point of 9,000 per cu. mm. Following the cerebral hemorrhage the terminal blood picture showed 14,000 mature granulocytes, 11,000 myelocytes, 7,000 lymphocytes and 60,000 monocytes. (See plate 3, figures 1 and 6, for the type of monocyte involved.)

With the hope of increasing the reserve of the patient's strength by attempting to establish the white count on a lower level with a more nearly normal differential, it was decided in July 1931 to institute arsenic therapy in the form of Fowler's solution. As is usual when this treatment is used in myeloid leukemia a definite increase in total count was noted during the first ten days of medication up to 42,000, the increase being specifically due to a relative and absolute increase of monocytes, from 60 per cent to 80 per cent of all cells, or from 14,000 to 34,000. Granulocytes and lymphocytes were essentially unaltered except that the granulocytes were decreased during the period of lowest total white counts (8,000) at the end of the period of medication. Starting with five drops three times a day the dose was gradually increased until the white count had been reduced to 20,650 by the end of the seventeenth day with a maximum dosage of 33 drops per day. Definite toxic symptoms appeared at this time. The medication was immediately stopped, and within the following 48 hours all acute symptoms had passed. The total white count at this time was 13,850. Three days later the white count reached its lowest level of 8,350, with 23 per cent neutrophiles, 1 basophile, 1 myelocyte, 22 per cent lymphocytes and 53 per cent monocytes. A rapid rebound in the total count and its constituent elements, more particularly the monocytes and myelocytes, carried the cells to a new high of 68,000 per cu. mm. during the ensuing two weeks with a return to the premedication equilibrium one week later.

During August and September the patient was in unusually good health and spirits. On September 26 he was suddenly seized with generalized convulsions in his home. The patient was immediately transferred to the Hospital where the convulsive seizures were readily controlled with luminal sodium. The white count on admission was 90,000 with 68 per cent very young monocytes. (Plate 3, figure 1.) The patient died in coma at 7:30 the following morning.

Postmortem examination was made by Dr. Ernest Scott, late Pathologist to the University Hospital, at 11:30 a.m. Nothing remarkable on external examination; no generalized adenopathy. The peritoneal lining was smooth and glistening. The liver was at the costal margin, normal in size and appearance except for some slight thickening of the capsule in places, with no gall-bladder lesion. The spleen measured 15 by 9 by 4 cm. and weighed 260 grams; it was brick red in color, firm with some mottling of the cut surface and an absence of follicles. The stomach, the small and large intestines, the pancreas, both adrenals and the prostate gland were normal to gross examination. The kidneys were normal in size; the capsules were adherent and there were cortical cysts measuring as much as 1.5 cm. in diameter; each kidney presented a dilated pelvis and thinned out cortex; both ureters were normal; the urinary bladder was normal. The pleural cavities were free of adhesions and showed no increased fluid. The lungs were air containing throughout; the vessels and bronchi at the hilus were normal; an old scar was found at the right apex but no evidence of tuberculosis was present. The hilus lymph nodes were

---

PLATE I

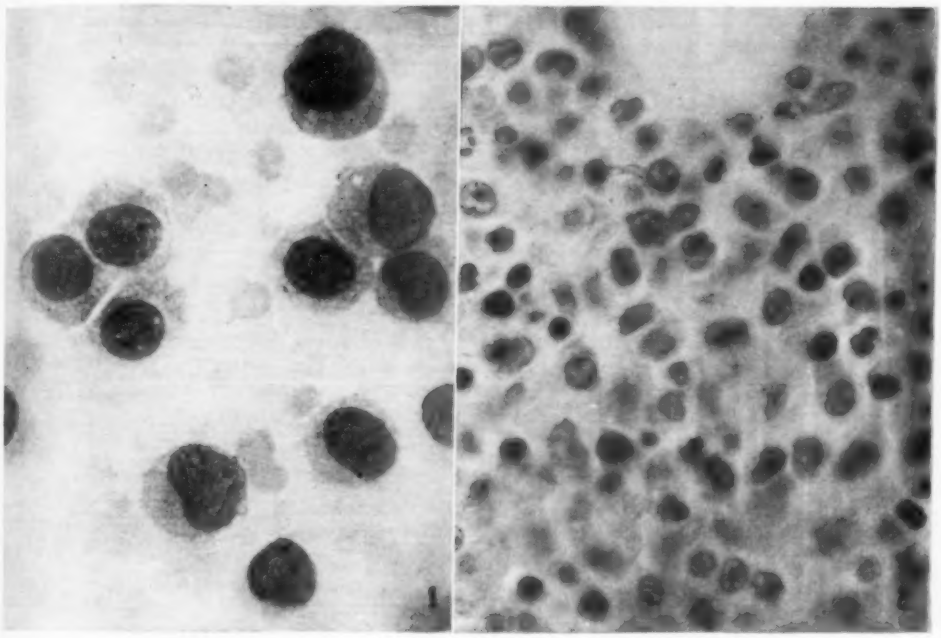
FIG. 1. Photograph of blood film stained with Wright's-Giemsa taken from Case II during the terminal leukemic phase. Monoblasts and young monocytes, one showing a small vacuole, make up the entire leukocytic picture of this field. × 960.

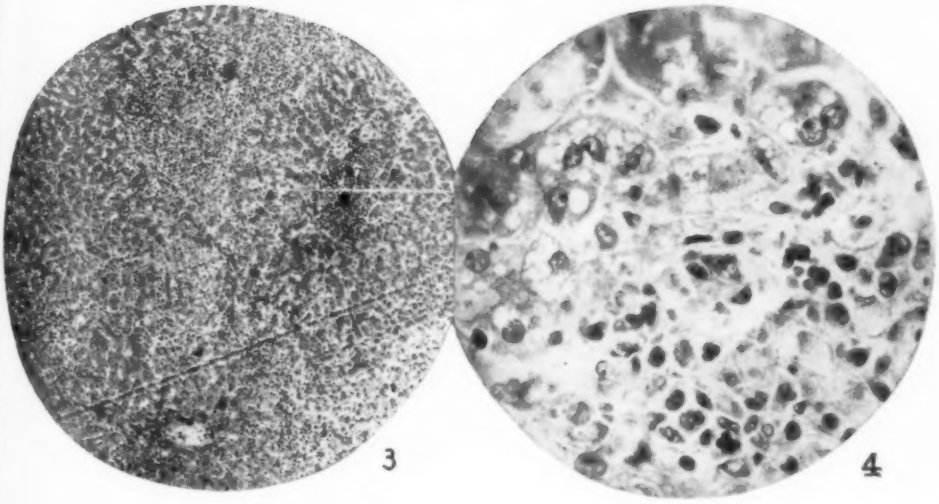
FIG. 2. Case I. Chronic monocytic leukemia. Photomicrograph of the femoral bone marrow showing the hyperplasia of monocytic elements with typical nuclear characteristics. Oil immersion, × 960 H. and E.

FIG. 3. Case VIII. Acute monocytic leukemia. Foci of monocytic cells scattered throughout the liver, more frequently periportal in location. Low power × 100.

FIG. 4. Case VIII. A higher power of the liver of figure 3, showing the character of the cellular proliferation. The monocytic hyperplasia is encroaching upon the liver cells which show large cytoplasmic vacuoles and evidence of nuclear degeneration. Oil immersion, × 960.

PLATE I





anthracotic but not enlarged. The mediastinal nodes were not remarkable. The heart weighed 500 grams; there was a moderate increase of pericardial fluid, no adhesions; the valves were intact. Bone marrow, secured from ribs, sternum, vertebra and femur, was everywhere abundant, dark red in color, and apparently hyperplastic. The scalp, calvarium and dura mater presented no noteworthy changes. Upon examining the hemispheres, however, the left frontal lobe was seen to be definitely enlarged, extending beyond the midline, compressing the inner surface of the right hemisphere, the convolutions being flattened and the sulci greatly narrowed over the surface. There was a congestion of the capillaries of the pia; the vessels at the base and the basilar and internal carotid arteries showed moderate sclerotic changes. Upon section after fixation a large blood clot filling the entire anterior horn of the left lateral ventricle and involving all of the adjacent tissue was found, being limited by a very thin margin of brain substance.

Microscopic Examination: Supravital preparations of the fresh tissues as well as fixed sections were studied. *Brain:* The vessels of the cerebellum and medulla were thickened and their lumen filled with masses of mononuclear cells. In the margin of the clot were to be found many monocytes singly and in large clumps. At some distance from the main hemorrhage there were areas of monocytic cells in the brain substance, many of which were surrounded by definite small hemorrhages. *Liver:* Sections showed an early cirrhosis, venous congestion and small accumulations of monocytes. *Spleen:* The Malpighian bodies were practically obliterated by the hyperplasia of large clear mononuclear cells with vesicular nuclei of varying size and contour and number, and by hemorrhage. There were many eosinophiles and some increase in fibrous tissue. The histo-pathologic picture was not unlike that seen in Hodgkin's disease. *Lymph Nodes:* As many lymph nodes as could be found, including axillary, mesenteric, retroperitoneal, mediastinal and peri-bronchial, were studied, all showing approximately the same pathologic changes: decrease or absence of normal lymph follicles, hyperplasia of large mononuclear cells with bizarre shaped vesicular nuclei, some increase of reticular and fibrous tissue and very many eosinophiles, with an occasional tissue basophile and plasma cell. (See figures 7 and 8, plate 2.) As in the case of the spleen the resemblance to Hodgkin's pathology was striking. *Bone Marrow:* All marrows showed a non-erythropoietic hyperplasia with a diminution in the usual fat content. Intimately intermingled with the myelocytic elements were small groups of monocytes, not present under normal conditions, with the characteristic nuclear abnormalities which suggest a disordered division mechanism. (See figure 2, plate 1.) Erythropoiesis and myelopoiesis were apparently progressing in an orderly sequence except that the myeloid cells showed a greater shift to the left with more of the early myelocytes and myeloblasts present than occur under strictly physiologic conditions. *Kidneys:* Sections showed advanced arteriosclerotic changes, but no monocytic foci

---

PLATE II

FIG. 5. Case VI. Acute monoblastic leukemia. Photomicrograph of femur bone marrow showing three mitotic figures and the monocytic replacement of myeloid and erythropoietic tissue. Note absence of usual fat cells. Oil immersion, × 960.

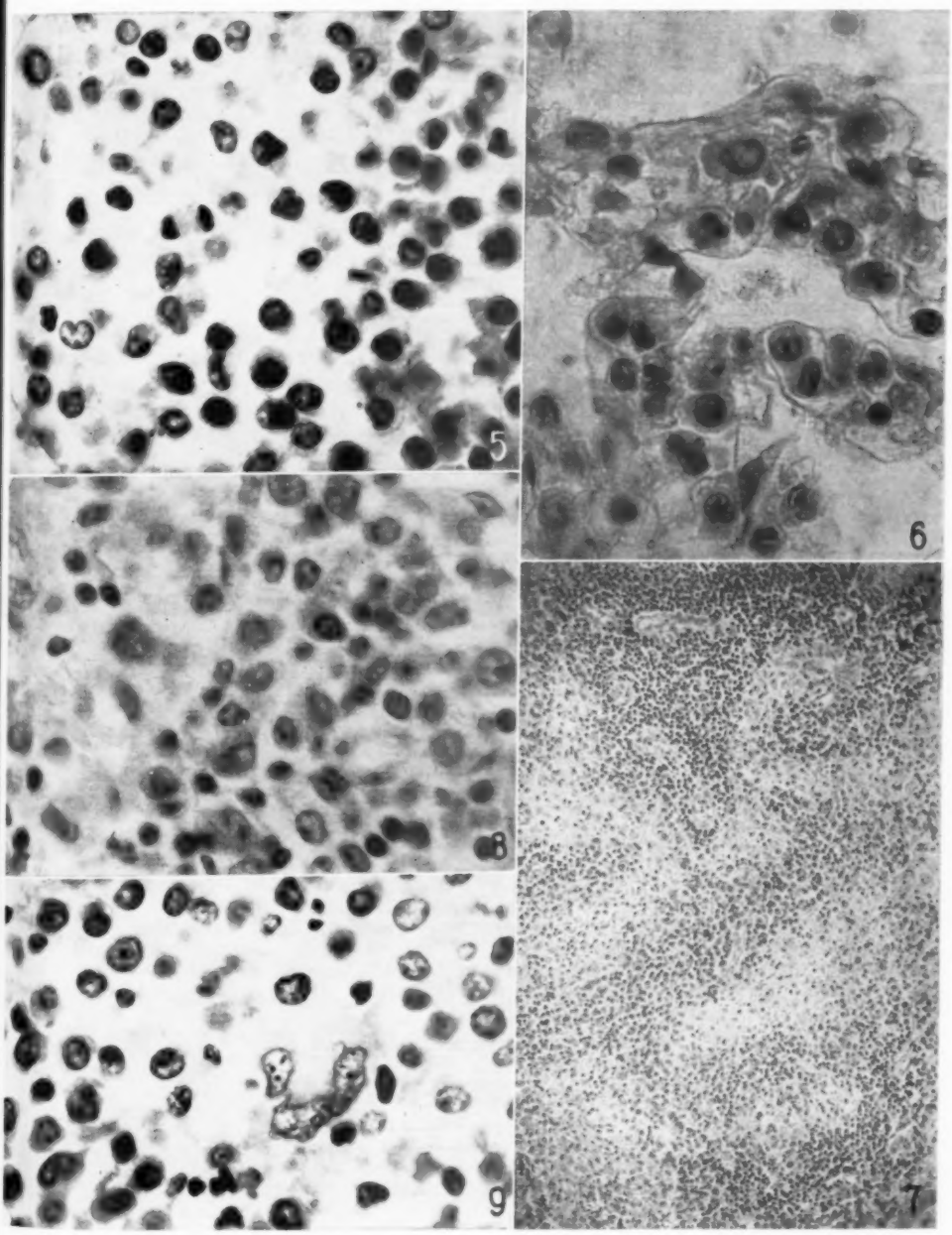
FIG. 6. Case VIII. Acute monocytic leukemia. Photomicrograph of the lung showing intraseptal proliferation and accumulation of monocytic elements with characteristic nuclei. Oil immersion, × 960.

FIG. 7. Case I. Chronic monocytic leukemia. Axillary lymph node showing the disordered architecture of the gland with almost complete replacement by monocytes and fibroblasts of normal follicles and germinal centers. 16 mm. objective, × 100.

FIG. 8. Case I. Higher power of the lymph node of figure 7, showing the character of the cells which have displaced the lymphatic elements. Oil immersion, × 960.

FIG. 9. Case VI. Acute monoblastic leukemia. Bone marrow from the tibia to contrast the monoblastic cells with a megacaryocyte. Oil immersion, × 960.

PLATE II



other than the intravascular accumulations of cells. *Adrenals:* An adenoma of the adrenals was revealed on microscopic examination. *Lungs:* The alveoli in certain areas were filled with a serous exudate with some neutrophilic leukocytes and fibrin. Other tissues were not remarkable from the standpoint of the monocytic dyscrasia.

In summary, we have a case in which all of the essential criteria for a chronic monocytic leukemia were met. The patient was followed through a 12 months' period without leukemic exacerbation and postmortem confirmation was obtained of death from cerebral hemorrhage upon a hypertensive arteriosclerotic basis. No active tuberculous focus was found. The tissue evidence, particularly in the bone marrow, spleen and lymph nodes, substantiated the existence of a relatively benign leukemic process primarily involving the monocytic strain of cells.

A very similar case has been studied by Dr. Hildegard Henderson, formerly associated with us in this laboratory, now of San Francisco, California. The patient, a white female aged 53 years, was first seen in July 1930 with complaints of sharp pain on the right side radiating to the back, night sweats, and easy fatiguability. The menopause had occurred five years previously. Two months before admission there had been profuse vaginal bleeding which persisted for two weeks and was followed by tarry stools for two weeks. A peri-nephritic abscess, yielding *B. coli*

PLATE III

Maturation of the monocyte as illustrated from selected cases of monocytic leukemia. The maturation of the monocyte and its life cycle have been followed under normal conditions and in experimental tuberculosis, and the evidence now accumulated in the study of monocytic leukemia is supplementary to and in complete conformity with that already adduced. All cells are drawn from Wright's-Giemsa stained blood films.

FIG. 1. Case I. Monoblast representative of the type of cell which appeared in increased numbers in the peripheral blood following cerebral hemorrhage in a case of chronic monocytic leukemia otherwise showing no exacerbation during a year's observation. Dense blue cytoplasm, purple mottled nuclear chromatin, fairly large spherical nucleoli. Size 14.5 microns.

FIG. 2. Case II. Monoblast of slightly later stage than figure 1 with the dense basophilia partly lost. No azurophilic granules are to be seen but the nucleus is typical. This cell and that of figure 3 were characteristic of the terminal stage in a case which 5 months previously had shown an aleukemic phase. Size 15.2 microns.

FIG. 3. Case II. Monoblast with large single nucleolus, but a cytoplasm less densely basophilic than in the two preceding cells. Some mottling of the cytoplasm and a suggestion of beginning vacuolation may be seen, but still no azurophilic granulations. This cell is typical of the majority of monoblastic cells seen in the peripheral blood in the acute stages of the disease. Size 17.5 microns.

FIG. 4. Case VI. Young monocyte with two nuclei in an acute case. A few, fine azurophilic granules may be seen in the cytoplasm. Multinucleated monocytes are encountered frequently both in the blood and in the tissues in monocytic leukemia. Size 16.1 microns.

FIG. 5. Case V. Vacuolated monocyte, a constant finding throughout the five months' duration of the disease in this case, both in the earlier aleukemic phase and in the terminal acute leukemic exacerbation. Vacuolation occurs much more frequently in the monocyte and in the leukemic monocyte than in the other types of white blood cells. Size 16.8 microns.

FIG. 6. Case I. Normal adult monocyte with characteristic indented nucleus and fine azurophilic granulations; this was the predominating type of cell present throughout the period of observation of a year in this patient during all of which time there was a definite elevation of the total leukocyte count with idiopathic monocytosis. Size 16.8 microns.

PLATE III

was found and surgically treated without sequelae or complications. The blood studies at this time showed a total white count ranging from 6,000 to 13,000 with neutrophilic leukocytes 24–43 per cent, lymphocytes 20–40 per cent, monocytes 25–28 per cent; red blood cells 3,470,00, hemoglobin 72 per cent. Since that time the monocytes have gradually increased. In March of this year, the total count was 11,350 and the hemoglobin 85 per cent; our differential from the blood films furnished by Dr. Henderson showed: neutrophilic leukocytes 5 per cent, basophiles 1 per cent, faintly basophilic lymphocytes (0) 4 per cent, moderately basophilic lymphocytes (M) 10 per cent, deeply basophilic lymphocytes (Y) 19 per cent, mature monocytes (some vacuolated and some with two nuclei) 57 per cent, young monocytes 2 per cent, non-phagocytic clasmatocytes 1 per cent. No adenopathy and no splenomegaly have been observed at any time. No tuberculous activity can be demonstrated. Aside from an increasing ease of fatiguability and "nervousness" there are no complaints. The profound neutropenia is significant as is the "shift to the left" in the lymphocyte formula. A chronicity of the process continues, whatever may be the underlying pathology, and whether the gradually increasing monocytosis without a definitely elevated total count is reflecting a leukemic proliferation of these elements in the bone marrow must await perhaps further studies. No other diagnostic entity can explain the picture at the present time.

Monocytic Leukemia with Aleukemic Phase; Leukemia Cutis

Case 2. Through the courtesy of Dr. Louis I. Mitchell, of Newark, Ohio, we have been permitted to follow the course of events in a man, W. W. P., aged 63 years, a railroad engineer, whose final illness began with skin manifestations and a leukopenia and terminated some five months later in a typical leukemic exacerbation of monocytic character. Dr. Mitchell is reporting this case in detail elsewhere, so that only a brief résumé will be presented here. In December 1931 the patient became conscious of a definitely increasing weakness and anemia. The following April he first noted the appearance of subcutaneous hemorrhagic areas on the inner aspect of each thigh, and at about the same time multiple small firm subcutaneous nodules developed over the lower abdomen, subsequently appearing over the body generally, including the scalp. The testes became enlarged and painful. When first seen by Dr. Mitchell early in April some 200 firm, discrete, movable, subcutaneous nodules were counted. There was no general adenopathy and the liver and spleen were not palpable. Temperature 98° F., pulse 80, respirations 20, blood pressure 120 systolic and 70 diastolic. All search for focal infection resulted in negative findings except for one molar tooth which was immediately extracted without untoward sequelae. Renal function was normal; urine was negative. The total white count was within the limits of normal, 5,000; the differential count revealed 30 per cent qualitatively normal monocytes, 28 per cent lymphocytes, 37 per cent neutrophiles, 2 per cent basophiles and 3 per cent eosinophiles. While myelocytes were not observed on this first count every subsequent differential showed from 2–9 per cent myelocytes. There were 3,000,000 red blood cells and 7.6 gm. hemoglobin per 100 c.c. blood; the erythrocyte fragility was normal, 0.396–0.300; the sedimentation velocity 20 mm. in one hour.

Under arsenic therapy in the form of sodium cacodylate, ¾ gr. subcutaneously every 48 hours, a definite reduction in the number and size of the nodules was noted with subjective clinical improvement in the patient, although a more profound leukopenia developed with both neutrophiles and monocytes obliterated from the picture for a time (chart 2). Shortly, however, more nodules began to appear even while the earlier ones were fading, and roentgen-ray and radium therapy were instituted on May 10, eleven treatments in all being given during the succeeding

three weeks. Again initial but only temporary success in reducing what a biopsy had shown to be aggregations of mononuclear cells in the deeper layers of the skin attended this therapy. By July the nodules were found to have become resistant to the measures instituted and during the latter part of this month a marked exacerbation of clinical symptoms occurred accompanied by evidences of a rapid increase in the size of liver and spleen. We were again permitted by Dr. Mitchell to study this patient in the terminal stage of his disease, in which the profound anemia and thrombopenia with hemorrhagic diathesis, and definite leukemic blood

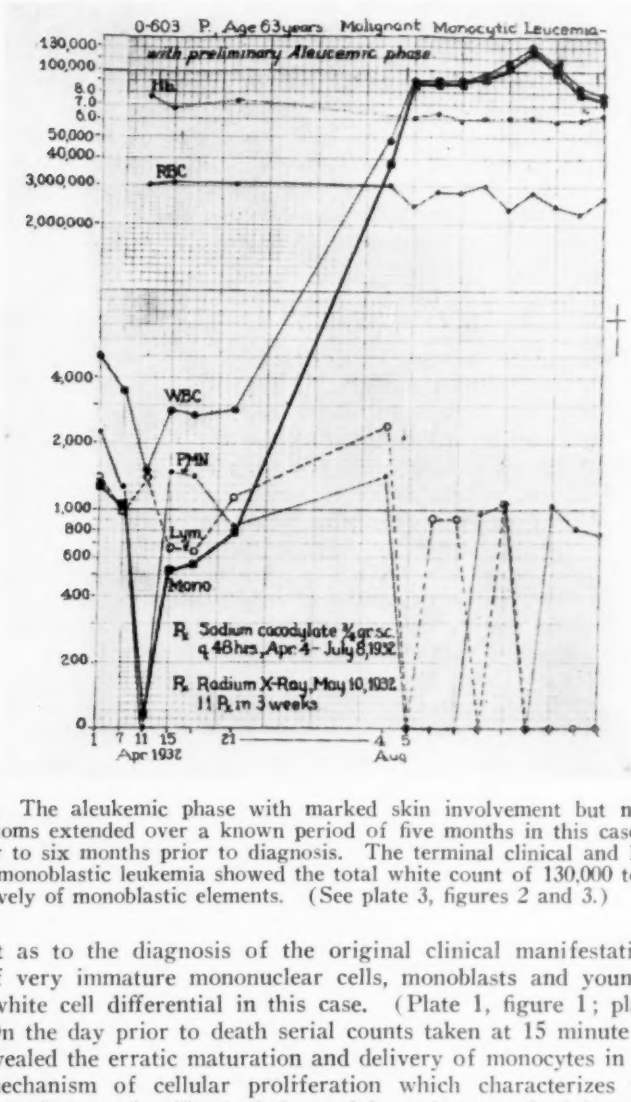


CHART 2. The aleukemic phase with marked skin involvement but minimal constitutional symptoms extended over a known period of five months in this case and probably for some four to six months prior to diagnosis. The terminal clinical and laboratory picture of acute monoblastic leukemia showed the total white count of 130,000 to be comprised almost exclusively of monoblastic elements. (See plate 3, figures 2 and 3.)

left no doubt as to the diagnosis of the original clinical manifestations. A predominance of very immature mononuclear cells, monoblasts and young monocytes, marked the white cell differential in this case. (Plate 1, figure 1; plate 3, figures 2 and 3.) On the day prior to death serial counts taken at 15 minute intervals for two hours revealed the erratic maturation and delivery of monocytes in an absolutely disordered mechanism of cellular proliferation which characterizes the leukemic state.[44] The erythrocyte fragility had changed from the normal of five months before to the leukemic range, 0.471–0.341; the icterus index was 9; the erythrocyte hematocrit was 27, the leukocyte packed cell volume 6.

The tissues secured at a partial postmortem by Dr. Mitchell and forwarded to this laboratory for section and study confirmed the clinical and laboratory diagnosis of monocytic leukemia. Liver, spleen, bone marrow and lymph nodes have proved in all cases thus far studied in this series to be of greatest significance from a pathologic standpoint. The liver and spleen in this patient were markedly enlarged. The liver revealed on microscopic examination marked hyperplasia of typical large mononuclear cells with vesicular nuclei of bizarre shape and number with usually one, never more than two, nucleoli. The normal architecture of the spleen was completely destroyed by the overgrowth of monocytic cells, comparable in all respects to the cells found in the circulating blood, in the skin nodules at biopsy and in the other organs mentioned at autopsy. The bone marrow everywhere was hyperplastic with non-hemoglobin bearing elements, the leukemic cells being quite distinct morphologically from the myelocytic cells among which they were scattered and upon which their rapidly proliferating mass was obviously encroaching.

This case exemplified three interesting manifestations of monocytic leukemia: (1) initial chronicity, (2) an initial leukopenic or aleukemic phase, (3) spontaneous, specific, widespread proliferation in the general connective tissues of an indigenous connective tissue element, the monocyte, at a time when the absence of any excess of these cells in the peripheral blood eliminated the possibility of an infiltrative mechanism to explain the formation of the subcutaneous nodules. This last evidence is akin to that obtained in the experimental studies of tuberculosis, in which tissue and organ proliferation of monoblasts, monocytes and epithelioid cells definitely precedes the appearance of increased numbers of monocytes in the peripheral circulation. This sequence of events holds both for the disease itself,[12] and for the reactions following the exhibition of tuberculo-phosphatid into the body.[2]

Cases 3 and *4* have been studied through the courtesy of Dr. S. T. Mercer, of the Vanderbilt Clinic, the Medical Center, New York City, who recognized and diagnosed the blood dyscrasia and its type in these two patients from the clinical history and character of the skin lesions, the latter having presented as one of the chief complaints in the syndrome. Both were acute cases of rather short duration, with no preceding illness, and with definite leukemic blood pictures of typical, characteristic monocytic dominance. One of these patients we saw in person, and had the opportunity of studying the supravital characteristics of the cells of the blood, as well as those presented in the fixed films. The other was studied only through the fixed blood films and the sectioned material secured at biopsy when representative skin nodules were obtained. The findings already listed as cytologically significant in monocytic leukemia were all present in these cases and the detailed data important to the recognition of monocytic leukemia cutis and its differentiation from the skin lesions in leukemic states of other cytologic origin and from non-leukemic dermatoses, are being presented by Dr. Mercer elsewhere.

Case 5 is again a case referred to us for an opinion as to the differential diagnosis by Dr. E. W. Mitchell of Cincinnati, Ohio. Dr. Mitchell kindly furnished us with a series of blood films covering the period of observation from June 15, to December 15, 1933, showing the gradual transition from an initial aleukemic state into the terminal leukemic syndrome of typical monocytic predominance. (Chart 3.) The history and clinical course are quite similar to those of Case 2, except for the absence of skin manifestations; the duration of the disease in each instance

was between five and six months. From the very beginning in this case, a careful survey of the cells in the peripheral blood revealed not only a relative increase in the number of monocytic cells but also qualitative changes which could not be mistaken. As is so much more frequently found with monocytes than with the other white blood cells, very many of these specific elements showed large, clear, vacuolar

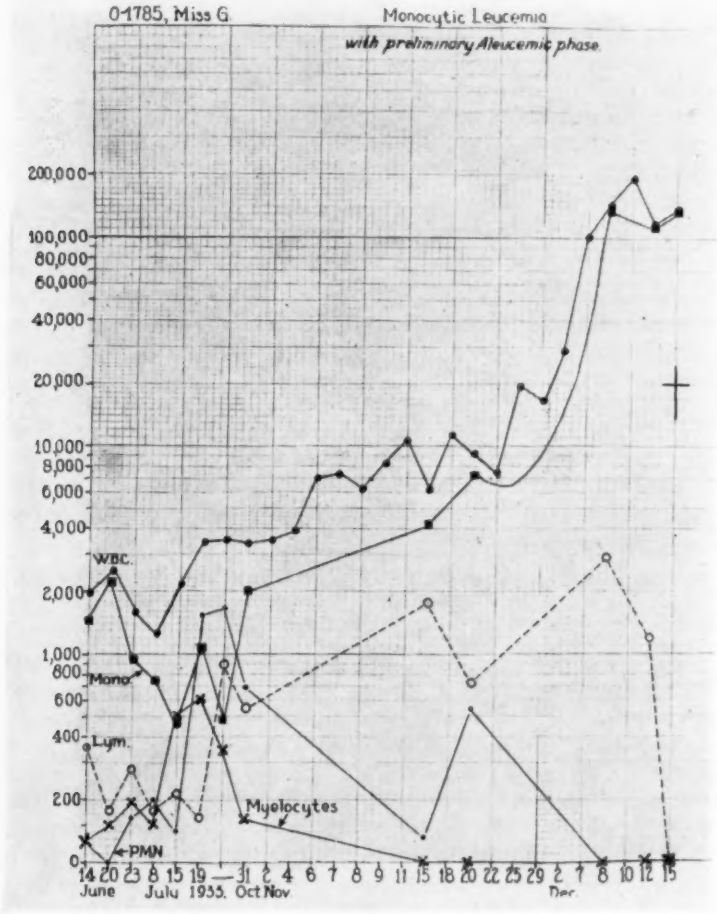


CHART 3. During the aleukemic as well as in the leukemic phase of this case the qualitatively changed and characteristic monocytes (see plate 3, figure 5) dominated the differential count. Myelocytes were present in the earlier months but disappeared as did most of the non-monocytic elements in the terminal stages of the disease, indicating extensive bone marrow invasion and replacement. The lymphocytes remained present longer and in more nearly normal total numbers than did the granulocytes.

degenerations. (Plate 3, figure 5.) Characteristic nuclear chromatin and cytoplasmic turbidity with azurophilic dust completed the identification. In the beginning myelocytes were present but as the peripheral count rose both mature neutrophiles and myelocytes steadily decreased in relative and absolute numbers, the lymphocytes not so markedly.

It is important both from the standpoint of prognosis and of treatment to separate such cases as this one from the Schultz syndrome of agranulocytosis and from other leukopenic states,[70] and this may best be accomplished by an adequate qualitative study of the white cells.

Acute Monocytic Leukemia

Our cases of fulminant monocytic leukemia have presented the typical acute manifestations with which the physician is beginning to be familiar, since the great majority of case reports now appearing in the medical literature deal with this striking symptomatic syndrome, which calls for immediate hospitalization and emergency measures.

Case 6. G. S., white female, aged 34 years, was first admitted to University Hospital, June 27, 1931 complaining of drowsiness, headache, fever (104° F.) and photophobia, of one week's duration with a loss of eight pounds in weight during this period. Past history was entirely negative. Family history has no bearing upon this or the subsequent illness. Physical examination: temperature 99° F., pulse 88, respirations 20, blood pressure 118 systolic and 70 diastolic. The mouth showed considerable dental work but teeth and gums were in good condition. There was no lymphadenopathy. The thyroid gland was enlarged and nodular, especially on the right side. The chest, abdomen, and extremities were negative. The urine examination was negative; the Wassermann and Kahn tests negative; the basal metabolic rate minus seven. Total white cells, 11,250; differential-neutrophilic leukocytes 70 per cent, lymphocytes 29 per cent, monocytes 1 per cent; total red cells 4,520,000, hemoglobin 75 per cent (Dare). On discharge July 1, 1931 the diagnosis was acute upper respiratory infection, adenoma of thyroid, non-toxic.

On December 12, 1932, 17 months later, the patient again sought admission to the University Hospital with the complaint of severe oral infection. Early in November the patient had suffered from tonsillitis followed by an otitis media which had ruptured spontaneously and drained. In the middle of November gingival abscesses about the first and third upper molars were surgically drained. Before the end of the month she had had seven abscesses incised by her dentist. The oral involvement grew steadily worse until finally a medical consultation was advised.

The patient when admitted December 12 was obviously acutely ill. An extensive necrotizing process had invaded the left maxilla; practically all teeth both above and below appeared to be involved with a purulent gingivitis, and the breath was markedly offensive. The jaws could only be opened a fraction of an inch. The cervical nodes were greatly enlarged, painful and tender. At the time of admission she had been menstruating profusely for eight days and gave a history of 10 days of profuse hemorrhage following the onset of the previous menses (November 3). Frequent chills and fever had been experienced since the onset of the present illness with persistent nausea and on two occasions vomiting. The temperature on admission was 102.4° F. The following day the temperature reached 104° F.; and for the most part this elevation (104° to 105°) was maintained throughout the course of the disease. The pulse ranged from 120 to 150; the respirations from 30 to 50. The blood pressure was 110 systolic and 58 diastolic. Moderate enlargement of the lymph nodes in all parts of the body was noted. The nodular cystic thyroid found on a previous admission was confirmed. The chest was essentially negative. The spleen was palpable and tender 6 cm. below the left costal border; the liver was not palpable. There were no other palpable masses and no areas of tenderness. Reflexes and extremities were negative. The white count on admission was 99,000

with 68 per cent young monocytes (plate 3, figure 4), 2 per cent monoblasts, 5 per cent mature active polymorphonuclears, 16 per cent myelocytes with none younger than the myelocyte "B" stage, 8 per cent small and 1 per cent intermediate sized

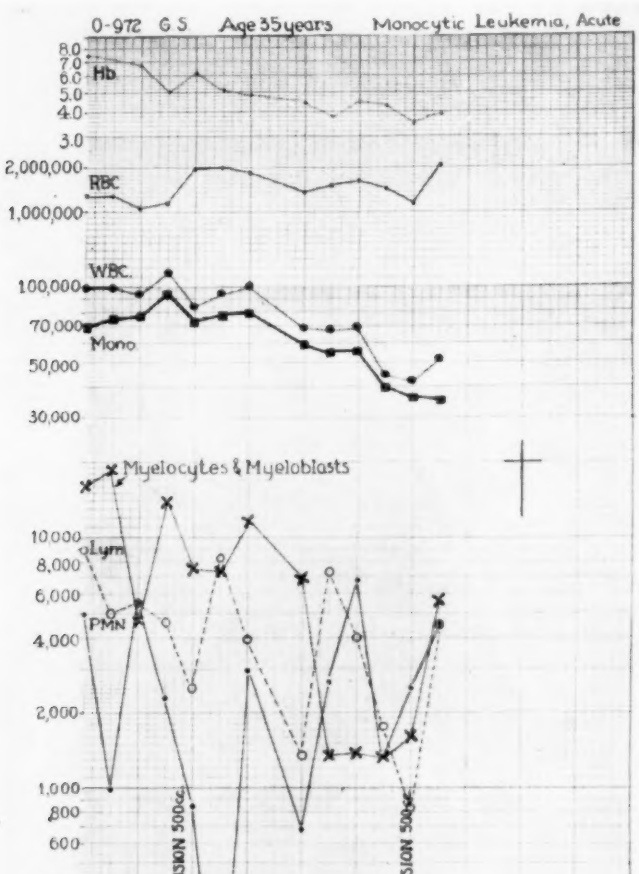


CHART 4. This graph depicts the blood findings in a patient with an acute, rapidly fatal, fulminant type of the disease, of six weeks' duration only, with monoblasts dominating the peripheral blood picture, 90,000 per cu. mm., but with severe anemia and myeloblasts and myelocytes present to the extent of from 10,000 to 20,000 per cu. mm., indicating progressive bone marrow invasion without complete replacement.

lymphocytes. See chart 4 for a summary of the blood findings in this case during the period of hospitalization. The total red cells were 1,310,000, hemoglobin 7.4 gm. per 100 c.c. blood; erythrocyte hematocrit 13, leukocyte packed cell volume 9;

erythrocyte sedimentation 75 mm. in 1 hour; fragility 0.471 to 0.300; icterus index 10; Wassermann negative; blood group, type IV. Blood sugar 38 mg. per 100 c.c. blood; NPN 40 mg.; uric acid 11.1 mg. Blood iodine 90 gammas % (normal 12).

Treatment consisted of two blood transfusions on December 15 and December 23 respectively; of two deep roentgen-ray exposures over the splenic area on December 17 and December 21; and of repeated large quantities of glucose-Ringer's solution intravenously. Death occurred on December 27, approximately six weeks from the first onset of symptoms referable to the leukemia.

Autopsy was performed December 28 by Dr. Harry Rinehart, Pathologist to the University Hospital. The anatomical diagnosis included: acute, diffuse, necrotizing, semi-membranous gingivitis, pharyngitis, tonsillitis, hemorrhagic cellulitis of the left cheek; bilateral diffuse, nodular thyroid with cystic degeneration and hemorrhage; acute suppurative cervical adenitis; generalized adenopathy of moderate degree; bilateral bronchopneumonia; parenchymatous degeneration of the heart; enlargement of the liver; splenomegaly; acute ulcerative colitis; pigmented areas of old hemorrhage in mucous membrane of ileum and cecum; recent hemorrhage in urinary bladder; chronic adhesive perimetritis; lacerations of the cervix; bilateral acute parenchymatous nephritis; bone marrow from humerus, femur, tibia, sternum, ribs, vertebra had the "gross appearance of that found in myelogenous leukemia"; edema of the meninges of the brain.

Microscopic examination revealed: *Bone Marrow:* The marrow everywhere was cellular, of a mottled gray color with very few normal appearing red areas. Supravital studies revealed practically complete absence of fat and of erythropoietic foci, and but one or two granular cells were found in each oil immersion field. A very rare megakaryocyte was seen. The hyperplasia was found to comprise chiefly medium sized mononuclear cells with large vesicular nuclei and a finely mottled cytoplasm, many mitotic figures reflecting the rapidity of the growth. Multinucleated cells were frequently encountered containing from two to five nuclei, not unlike the Dorothy Reed-Sternberg cells of Hodgkin's disease. The multinucleated cells were of the same type as the predominating mononuclear cells and the entire group were distinctly foreign to the normal cytology of bone marrow. Cover slip preparations of emulsions of marrow from humerus and tibia in autogenous blood plasma, stained with Wright's-Giemsa, confirmed the monocytic character of these cells. Fixed sections further established the identity of the cellular response in the marrow with that of the circulating monocytic cells of the blood. (Plate 2, figures 5 and 9.) *Lymph Nodes:* Fixed sections from the inguinal, iliac, lumbar, retroperitoneal, mesenteric, mediastinal, axillary and cervical nodes were studied. An atrophic thymus did not partake of the monocytic hyperplasia found elsewhere in lymphatic tissue. Hemorrhage was commonly encountered. The follicles were markedly atrophic with germinal centers either entirely absent or infiltrated with the large mononuclear elements, which also filled the sinuses. Monocytic mitoses and eosinophilic granulocytes were prominent. *Spleen:* Weight 650 grams; red, soft, smooth capsule; on cut section uniform reddish brown color with decided increase in pulp substance and an absence of visible Malpighian bodies. The architecture was markedly altered by the overgrowth of monocytic cells, which had invaded the lymph follicles and which filled the dilated sinuses; occasional myelocytes and clasmatocytes; many mitotic figures were found in the monocytic cells. *Liver:* Weight 2350 grams; extended 5 cm. below the costal border; showed parenchymatous degeneration, some focal mononuclear aggregations, and sinuses filled with monocytes. *Lungs:* Bronchopneumonia, edema with increased monocytes in alveolar septa and vessels, no evidence of tuberculosis. *Heart:* Weight 325 grams. No monocytic accumulations in tissue other than those within vessels. Moderate parenchymatous degeneration. *Pancreas* and *adrenal* normal. *Kidneys:* Monocytic infiltrations with

definite scarring and tubular degenerations; glomerular tufts and capillaries showed abundant monocytic cells. *Stomach, duodenum, jejunum* and *ileum* showed evidence of old and recent punctate hemorrhages; the colon was the seat of definite ulcerative necrotic lesions with polynuclear and monocytic infiltrations. The *brain* showed only an intravascular increase of monocytes without tissue increase.

In brief, as was to be expected, all organs and tissues showed the intravascular increase of monocytic cells, and in addition, in those places where connective tissue reticular "mesenchymal rests" exist normally, loosely organized foci of characteristically disoriented monocytic elements were found, proliferating wildly as judged from the numerous mitotic figures, and more or less completely displacing normal structures. Bone marrow, lymph nodes and spleen, the principal sites for blood cell generation, present the most marked pathologic changes in monocytic leukemia, thus serving to demonstrate still further the close relationship which exists between the three types of white blood cells and the possibility of a common ancestry.

Case 7. D. M., a white boy, aged five years, referred by Dr. A. G. Helmick, was admitted to the Research Service of the University Hospital November 2, 1933, complaining of increasing weakness, pallor and swollen glands. On September 5, 1933 the patient complained of sore throat and suffered a gastric upset. One week later definite cervical adenopathy was observed. During the following month the cervical nodes fluctuated from time to time in size. About the end of September the patient developed a severe upper respiratory infection with secondary sinus involvement. An increasing disinclination to normal activity, increasing pallor, persistent adenopathy and the development of mouth breathing led to the diagnosis of tonsils and adenoids. Fortunately, prior to operative interference a routine blood study was requested and the following report returned: PMN 3 per cent, lymphocytes 97 per cent, hemoglobin 30 per cent. It was at this point that we first saw the patient. Bleeding from the nose difficult to control had occurred on two occasions and oozing from the gums was becoming increasingly troublesome. Spontaneous subcutaneous hemorrhages had appeared in addition to a recently noted increased susceptibility to bruises.

The past and family histories were unessential.

On physical examination the patient revealed: temperature 100° F., pulse 128, respirations 28, blood pressure 104 systolic and 50 diastolic. The outstanding points were pallor, marked cervical adenopathy and a noisy type of mouth breathing. He was restless, active, but tired easily. Discolored areas were noted scattered over the entire body; the nail beds showed some cyanosis and the lips were dry and encrusted with dried blood. The conjunctivae were pale, but the eyes and eye grounds showed no hemorrhages. The nasal passages were occluded by excessive pharyngeal lymphoid hyperplasia; there was a posterior nasopharyngeal drip producing a gurgling type of mouth breathing, and necessitating frequent coughing; the tonsils were greatly hypertrophied with reddened pillars and small faucial isthmus. The gums were edematous, bleeding easily, and several small blood clots were seen about the teeth. A very fetid and offensive breath was apparent. On the dorsum of the posterior third of the tongue were two small hemorrhagic ulcers. The cervical nodes were prominent, firm, discrete, freely movable, not adherent to the skin, of variable size and slightly tender; the nodes at the angle of the mandible were largest, the submaxillary slightly smaller; those in the anterior triangle smaller than those in the posterior. The axillary nodes were about 2 cm. in diameter; the epitrochlears and inguinals were also readily palpable. The chest was negative. The spleen

was enlarged, firm, extending 4 cm. below the costal margin in the nipple line, but the liver margin was not definitely palpated. Genitalia, extremities and reflexes were normal.

Laboratory findings: Total white count 20,600; supravital differential PMN 5 per cent, PMB 7 per cent, PME 5 per cent, myelocytes 10 per cent, small lymphocytes, 19 per cent, monocytes 49 per cent, monoblasts, 5 per cent. Blood platelets 6000 per cu mm. Total red cells 760,000 hemoglobin 3.4 gm. per 100 c.c. blood, reticulocytes 3.2 per cent, hematocrit 9, erythrocyte fragility 0.412 to 0.300. The basal metabolic rate was plus 13. The sequence of events as reflected in the blood studies and the therapeutic measures employed may be followed from chart 5. Blood transfusion was performed as an emergency measure on admission and was repeated as often as was necessary during the succeeding weeks to control the hemorrhagic tendencies and provide a maintenance supply of red cells while attempts were being made to reduce the condition to a more chronic stage. Following the ineffectiveness of arsenic medication, roentgen-ray treatments were instituted and either a spontaneous exacerbation of the disease occurred or the irradiation actually accentuated the process. The total white count increased, the spleen and lymph nodes continued to enlarge, subcutaneous skin nodules appeared, and within one month death occurred. A postmortem examination was refused.

Myelocytes of the A, B, and C type were present at all times and an occasional myeloblast was encountered, but no irregularity in the division figures or in the symmetry of the nuclei and nucleoli characteristic of leukemic states was found. The lymphocytes were entirely within the qualitative range of normal at all times also, and the final exacerbation was reflected almost entirely in an increase in the monocytic elements.

The Problem of Mixed Leukemia

It will have been noted that in each of the cases cited in this series there have been recorded "shifts to the left" in both lymphoid and myeloid series. Nevertheless qualitative as well as quantitative data have been presented which suggest, and in four of the cases postmortem studies have confirmed, the primary incrimination of the monocyte rather than the other cell strains. Our remaining cases of monocytic leukosis have presented an even more striking mixture of cell types in the peripheral circulation, and undoubtedly represent the type of case which has been discussed in the literature as mixed leukemia. Certain pertinent data have been accumulated, however, which lead us to question a sound underlying pathologic basis for this clinical diagnosis. A mixed leukemia in which all three strains of white cells are equally involved is, of course, theoretically possible though unlikely, if our present concepts of their common stem cell origin are correct (diagram 1). It is only in so-called monocytic leukemia that we have encountered this liberal sprinkling of myelocytes and young lymphocytes, together with a monocytosis. In the classic myeloid or lymphoid syndrome the monocyte is never present in increased numbers, nor does it show peculiar qualitative changes, and usually the cell strain principally involved represents 95 to 99 per cent of all cells found in the blood. In the cases in which an equal quantitative distribution of the three strains of white cells has occurred in the blood with immature elements present from

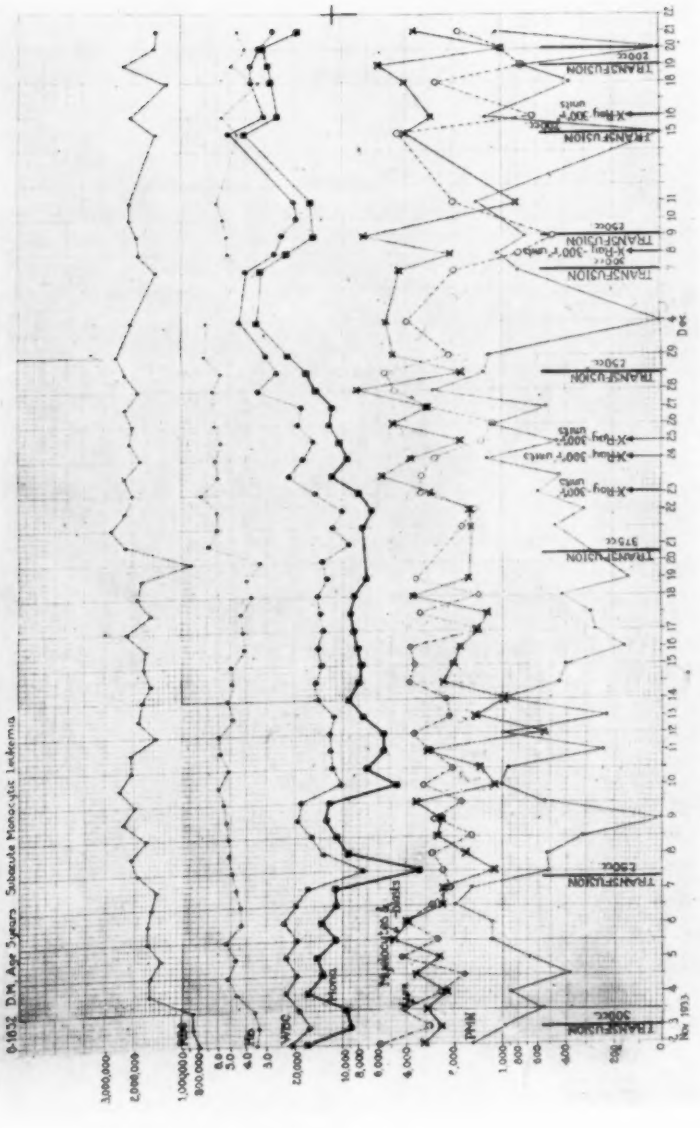


CHART 5. While the monocytic elements predominated throughout the acute course of the disease in this child, myelocytes and lymphocytes persisted in the peripheral blood in appreciable numbers. The severe anemia presenting when the patient was first seen was controlled by repeated blood transfusions. Following roentgen-ray therapy there was a definite increase in the total white count composed almost entirely of monocytes, and the clinical course was correspondingly more acute.

each, it has been possible, nevertheless, by applying the criteria now available for the appraisal of normal cellular development, as contrasted with abnormal and disordered maturation, to distinguish the primary from the secondary involvement.

We have illustrated elsewhere [44] the amitotic nuclear division occurring in the myeloid elements in subacute myeloblastic leukemia. In this series the same asymmetry and atypical cellular division were noted in the monocytes. All of the cellular elements in the circulation showed some mitotic activity in the cases of monocytic leukemia. It was only among the monocytes, however, that we noted unequal division of nucleoli and asymmetrical distribution of nuclear chromatin, incomplete mitotic spindles with resulting nuclei of unequal size. Both myelocytes and young lymphocytes divided normally and the resulting multinucleated cells contained symmetrical and equally divided nucleoli. At postmortem the wide dissemination of monocytic hyperplasia, particularly at the sites and at the expense of myeloid and lymphoid generation, further confirmed the interpretation of primary monocyte pathology implied from the studies of the peripheral blood. These points will be presented in detail elsewhere and represent a distinct contribution which we believe the study of monocytic leukemia can make to a better understanding of the fundamental metabolic or environmentally conditioned constitutional disturbances upon which the leukemic states are engrafted.

Etiologic Considerations

Although the nature of the disorder, which permits or causes leukemic hyperplasia of monocytes, is not known, the mechanism of monocytosis in other pathologic states is more apparent. In general, the existence of either or both of two circumstances has resulted in a stimulation to monocytic proliferation: (1) the opportunity or need for phagocytosis of non-pyogenic bacteria or of other particulate matter; (2) the presence of an excess of lipoidal substances, occasioned either by certain disorders in the normal metabolism of fats, or by the liberation in vivo, or the parenteral introduction, of foreign monocytogenic lipoids.

We have already cited instances in which the phagocytic function of this cell strain has formed the basis for increased activity, and the clear cut results obtained in the studies with tuberculo-phosphatid immediately suggest the monocytogenic potentialities of other lipoids. Conversely, the cellular reactions in certain diseases known to involve disturbances in lipoid metabolism appear to be largely of monocytic origin, though the evidence for strict cytologic identity is as yet inconclusive in some.

In certain cases of diabetic coma with lipemia, large foam cells not unlike hypertrophied monocytes may be found in the spleen and to a lesser extent in the lymph nodes, tissues normally the site of origin for monocytes. Of particular interest and probably of importance in considering this aspect of the problem is the apparent relationship of faulty lipoid metabolism to

monocytic proliferation as observed in the so-called xanthomatoses. In Niemann-Pick's disease large phagocytic cells storing lecithin and phosphatid and arising from the reticulum cells [71] are not only disseminated widely throughout the body in enormous numbers but may be found invading the blood stream. Whether this phenomenon is the result of a need for increased phagocytic function as suggested by Bloom [72] or represents a specific stimulus from the blood lipoid as suggested by the work on tuberculo-phosphatid and lecithin [2] is uncertain. A similar origin for the increased numbers of phagocytic cells noted in Hand-Schüller-Christian's disease is probable, the lipoid deposition and lipemia consisting chiefly of cholesterin-fatty esters.[73] The accumulation of fat-laden phagocytes in this disease forms a very characteristic granulation tissue which is readily converted into fibrous tissue, often causing severe anemia when it occurs in the bone marrow. The mechanism is not unlike that observed in Hodgkin's disease. In Gaucher's disease a lipemia consisting of the cerebroside, kerasin [74] results in the formation of lipoid storage cells in the tissues which are often multinucleated in type and suggest morphologically the giant cells of tuberculosis and Hodgkin's disease. In the monocytes of monocytic leukemia itself we have noted, as have others, the frequency with which vacuolar, fatty (?) degeneration is seen (plate 3, figure 5) in marked contradistinction to its occurrence in the cells in other types of leukemia.

Thus, tuberculosis, Niemann-Pick's disease, the Schüller-Christian syndrome, Gaucher's, and Hodgkin's disease, while differing clinically and pathologically, nevertheless have certain features in common. A generalized adenopathy with splenomegaly characterize the last four and may be present in tuberculosis. The development of granulomatous tissue with scar formation has been a common finding, more particularly in tuberculosis, Christian's disease and Hodgkin's disease. Large mononuclear, and multinucleated giant cells occur, being especially prominent in tuberculosis, Hodgkin's disease and Gaucher's disease. Some form of lipoid disturbance has been shown to be present in each of these conditions except Hodgkin's disease, and in each, phagocytic cells probably of the monocytic strain, have reflected the major cellular response.

In typical Hodgkin's disease the characteristic blood picture includes an absolute, as well as a relative, monocytosis, together with a leukopenia, lymphopenia, eosinophilia, and anemia, the reversed monocyte-lymphocyte ratio reflecting the hyperplasia of monocytes and fibroblasts in lymph nodes and frequently in bone marrow. The etiology is as yet unproved, but if the avian tubercle bacillus or other acid fast organism is involved, as has been suggested,[75, 76] the lipoid basis for the cellular pathology would be clear here also. Hodgkin's disease provides an interesting transition between the group of diseases showing monocytosis and the group of pathologic states which may be said to be leukemic in nature. The histopathology of lymph nodes and spleen from our cases diagnosed as monocytic leukemia (especially Case 1) was indistinguishable from that of typical Hodgkin's

disease. Subsequently we have found an instance in the literature [52] of Hodgkin's disease reported as terminating in monocytic leukemia. Dameshek [77] has noted the similarity between, and possible common etiology of so-called aleukemic reticulosis and Hodgkin's disease. It would seem that any approach to an understanding of the cellular reaction in Hodgkin's disease, the xanthomatoses and monocytic leukemia should be made with a full recognition of the basic studies on the mechanism of monocytosis in other diseases, more particularly those in tuberculosis with tuberculo-lipoids. This, of course, does not deny the possible neoplastic nature of some members of this group, but it does suggest an explanation of some of the features found in these diseases difficult to reconcile with the theory of malignancy.

Discussion

In any study involving the cells of the blood and the organs and tissues from which they arise, the principal difficulty commonly encountered at the present time is the adequate differentiation of the mononuclear elements. Under pathologic conditions a "shift to the left" in any or all of the cell strains complicates the picture still further, with monoblast, myeloblast and lymphoblast presenting a minimum of criteria for differential identification. In plate 3 may be seen the transitional stages in the maturation from monoblast to mature monocyte as observed with the Wright's-Giemsa staining technic in the blood of patients with monocytic leukemia. The monoblast embodies characteristics which after careful study by comparison and contrast with myeloblast and lymphoblast usually make for its definite recognition. The density of the basophilia of the cytoplasm (plate 3, figures 1, 2, 3) is midway between that encountered in the lymphoblast and the lighter blue of the myeloblast. Usually one nucleolus, never more than two spherical nucleoli, are found in the characteristic, purple staining, splotchy chromatin of the monocyte nucleus. Figure 2 is typically representative of the gradual reduction in basophilia of the cytoplasm, which occurs during the early stages of maturation, to a maintained, opaque, mottled, cytoplasmic background within which appear many fine, scattered azurophilic granules in the mature state. Multiple nuclei (figure 4) are frequently encountered and in most of the leukemic cases there are from few to many highly vacuolated cells among the monocytes (figure 5). In the more chronic states many of the monocytes are qualitatively entirely normal (figure 6). The monocytes in the peroxidase stain react positively but usually may be distinguished from the granulocytes in the amount and distribution of oxidase granules. In the supravital studies with neutral red and Janus green, which always should accompany and supplement the fixed film surveys, the characteristic surface film motility, scattered fine blue-green mitochondria and a rosette of neutral red vacuoles identify the monocyte. These finer cytological differentiations are not apparent upon superficial casual examination, but with experience become increasingly de-

pendable. The experimental studies in tuberculosis formed the basis for the first careful analysis of the life cycle of the monocyte, revealing the epithelioid " shift to the right " in that disease. The study of monocytic leukemia provides the material for a similar appraisal of the maturation phases in this strain of cells with variable degrees of " shift to the left " toward the monoblastic level revealed.

In those cases which have come to autopsy in our series we have studied the various tissues carefully in an attempt to ascertain the origin and nature of the new growth of cells responsible for the abnormal blood picture. Always the principal sites of cellular hyperplasia have been in lymphoid tissue, spleen, liver and bone marrow. Arising diffusely in intervascular areas the characteristic large mononuclear monocytes have been found scattered loosely between and more or less completely displacing the normal cells. Many mitotic figures may be found, and deeply indented vesicular nuclei, frequently multiple and of varying size within the same cell (plates 1 and 2), serve to produce a cytological picture in the tissues altogether different from that seen in either myeloid or lymphatic leukemia. Studies of normal monocytic differentiation in the spleen [13] and peripheral lymph nodes [14] and of pathologic proliferation in experimental tuberculosis or after the injection of the lipoid fractions from tubercle bacilli [2] have revealed the potentialities of latent connective tissue elements for monocytic differentiation when the proper stimuli are present. Fibrous connective tissue may also increase somewhat at times and the similarity between the pathologic tissue in monocytic leukemia and that found in Hodgkin's disease for example has at times been startling. The study of the five cases of monocytic leukemia coming to autopsy has served to reaffirm the evidence of the mesenchymal connective tissue origin of the monocyte adduced in the long series of studies already referred to in which this cell has been subjected to careful analysis. The fact that the monocytic hyperplasia in the leukemia of that type has occurred predominantly in those locations where the other white cell elements, myelocytes and lymphocytes, normally differentiate, further suggests the close relationship which we believe exists between the three strains of white cells in their earliest beginnings.

We have cited the wide range of clinical manifestations observed in our series of cases of monocytic leukemia, and the marked difference in acuteness and severity of the disease. This is, of course, in conformity with the observed facts in the other leukemic states and in disease in general. Either the etiologic factor varies in its severity or in the duration of its effect upon the tissues or, as seems more likely, the constitutional reaction of the individual provides the conditioning factor which determines in the last analysis whether the pathologic trend is to be rapidly progressive or relatively quiescent. Each patient must therefore be studied quite objectively and from other standpoints than the blood picture, before an intelligent prognosis may be given. Just where the dividing line between a so-called benign, idiopathic monocytosis and chronic monocytic leukemia

should be drawn is not always clear, but the benefit of the doubt should be given the patient as long as the diagnosis of leukemia carries with it the implications of a fatal malignancy.

Summary

1. Clinical studies are aiding, and in turn are being distinctly furthered by a proper evaluation of the monocyte.

2. The monocyte is an independent entity, with life cycle and functions specific to its own peculiar endowments.

3. In tuberculosis the monocyte has been shown to reflect, and to be an important part of, the cellular reactions to the acid fast bacilli and more particularly to the lipoids elaborated by this group of organisms. When properly appraised and interpreted in conjunction with the other cellular elements of the blood and in the further light of available clinical and laboratory data, prognosis in this disease and an accurate prompt estimation of the effectiveness of any given therapeutic measure become possible.

4. In Hodgkin's disease, syphilis, pneumonia, the xanthomatoses and in other pathologic states the monocyte if properly evaluated may contribute to the diagnosis of the disease and to the management of the patient.

5. During the past four years 12 cases of monocytic leukemia have been diagnosed and nine have been carefully studied clinically with five post-mortem surveys.

6. The problem of differentiating the leukemias and more particularly the question of mixed leukemia has been discussed and data submitted upon which to base judgment in the critical analysis of the individual patient.

We desire to acknowledge the assistance of our several Residents, Drs. S. T. Mercer, Lowell A. Erf, and Malcolm M. Hargraves, on the Research Service, University Hospital, in the care and study of individual cases in the series here reported.

BIBLIOGRAPHY

1. Cunningham, R. S., Sabin, F. R., Sugiyama, S., and Kindwald, J. A.: Rôle of the monocyte in tuberculosis, Bull. Johns Hopkins Hosp., 1925, xxxvii, 231.
2. Sabin, F. R., Doan, C. A., and Forkner, C. F.: Studies on tuberculosis, Suppl. 3, Jr. Exper. Med., 1930, 1–152.
3. Doan, C. A.: Newer aids to diagnosis and prognosis in tuberculosis, Med. Clin. N. Am., 1930, xiv, 279–299.
4. Blackfan, K. D., and Diamond, L. K.: Monocyte in active tuberculosis; supravital studies of blood, Am. Jr. Dis. Child., 1929, xxxvii, 233–243.
5. Morriss, W. H., and Tan, S. H.: Differential leukocyte count in pulmonary tuberculosis; value of lymphocyte-monocyte ratio in determination of activity, Am. Rev. Tuberc., 1927, xvi, 729–748.
6. Flinn, J. W.: Study of differential blood count in 1000 cases of active pulmonary tuberculosis, Ann. Int. Med., 1929, ii, 622–636.
7. Hickling, R. A.: Monocytes in pneumonia; clinical and hematologic study, Arch. Int Med., 1927, xl, 594–604.
8. Doan, C. A.: Clinical implications of experimental hematology, Medicine, 1931, x, 323–371.

9. MERCER, S. T.: Preliminary observations on human blood in early syphilis by supravital method, Proc. Soc. Exper. Biol. and Med., 1931, xxviii, 1033–1035.
ROSAHN, P. D., and PEARCE, L.: Blood cytology in untreated and treated syphilis, Am. Jr. Med. Sci., 1934, clxxxvii, 88–100.
10. MICHAELIS, L., and WOLFE, A.: Über Granula in Lymphocytes, Virchow's Arch. f. path. Anat., 1902, cxlvii, 151.
11. PAPPENHEIM, A., and FERRATA, A.: Über die verschiedenen lymphoiden Zellformen des normalen und pathologischen Blutes, Folia haemat., 1910, x, 1.
12. DOAN, C. A., and SABIN, F. R.: Local progression with spontaneous regression of tuberculosis in bone marrow of rabbits, correlated with transitory anemia and leukopenia after intravenous inoculation, Jr. Exper. Med., 1927, xlvi, 315–341.
13. CUNNINGHAM, R. S., SABIN, F. R., and DOAN, C. A.: The differentiation of two distinct types of phagocytic cells in the spleen of the rabbit, Proc. Soc. Exper. Biol. and Med., 1924, xxi, 326–329.
14. FORKNER, C. E.: Material from lymph nodes; heterology of lymphoid tissue with special reference to the monocyte, Jr. Exper. Med., 1929, xlix, 323–345. Origin of monocytes in certain lymph nodes and their genetic relation to other connective tissue cells, *ibid.*, 1930, lii, 385–403.
15. BLOOM, W.: Hemopoietic potency of small lymphocyte, Folia haemat., 1926, xxxiii, 122–131. Origin and nature of monocyte, *ibid.*, 1928, xxxvii, 1–62.
16. SCHILLING-TORGAU, V.: Das Blutbild und seine klinische Verwertung, 1912, G. Fischer, Jena.
17. RESCHAD, H., and SCHILLING-TORGAU, V.: Über eine neue Leukämie, durch echte Übergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr., 1913, lx, 1981–1984.
18. WISEMAN, B. K.: Criteria of age of lymphocytes in peripheral blood, Jr. Exper. Med., 1931, liv, 271–294.
19. RANVIER, L.: De l'origine des cellules du pus et du rôle de ces éléments dans les tissus enflammés, Compt. rend. Acad. d. sci., 1891, cxx, 922–926.
20. METCHNIKOFF, E.: Untersuchungen über die mesodermalen Phagocyten einiger Wirbeltiere, Biol. Centralbl., 1883, iii, 560.
METCHNIKOFF, E.: Leçons sur la pathologie comparée de l'inflammation, 1892, G. Masson, Paris.
21. MARCHAND, F.: Reference über die Beteiligung der Leukozyten an der Gewebeneubildung, Behandl. d. 10 Intern. Med. Kongr. z. Berlin, 1890, ii, 9.
22. MAXIMAW, A.: Experimentelle Untersuchungen über die entzundliche Neubildung von Bindegewebe, Beitr. z. path. Anat. u. allg. Path., Suppl., 1902, v, 1.
23. RIBBERT, H.: Die Abscheidung intravenos injizierten gelosten Carmins an den Geweben, Ztschr. f. allg. Physiol., 1904, iv, 201.
24. GOLDMANN, E. E.: Die äussere und innere Sekretion des gesunden und kranken Organismus im Lichte der vitalen Färbung, Beitr. z. klin. Chir., 1909, lxiv, 192–265.
25. ASCHOFF, L., and KIYONO, K.: Zur Frage der grossen Mononukleären, Folia haemat., 1913, xv, 383–390.
26. LEWIS, M. R.: Formation of macrophages, epithelioid cells from leukocytes in incubated blood, Am. Jr. Path., 1925, i, 91–100.
LEWIS, M. R., and LEWIS, W. H.: Transformation of mononuclear blood cells into macrophages, epithelioid cells and giant cells in hanging drop blood cultures from lower vertebrates, Contrib. to Embryol., Carnegie Inst., 1926, xviii, 95.
LEWIS, W. H.: Harvey Lectures, 1925–26, xli, 77.
27. BAKER, L. E.: Cultivation of monocytes in fluid medium, Jr. Exper. Med., 1933, lviii, 575–583.
28. DOAN, C. A., and SABIN, F. R.: Normal and pathological fragmentation of red blood cells, . . . the correlation of the peroxidase reaction with phagocytosis in mononuclear cells, Jr. Exper. Med., 1926, xliii, 839–850.

29. Doan, C. A., and Sabin, F. R.: Local progression with spontaneous regression of tuberculosis in bone marrow of rabbits, correlated with transitory anemia and leukopenia after intravenous inoculation, Jr. Exper. Med., 1927, xlvi, 315–341.
30. Sabin, F. R., and Doan, C. A.: Presence of desquamated endothelial cells; so-called clasmatocytes in normal mammalian blood, Jr. Exper. Med., 1926, xliii, 823–837.
31. Sabin, F. R., Doan, C. A., and Cunningham, R. S.: Discrimination of two types of phagocytic cells in the connective tissues by the supravital technic, Carnegie Inst. of Washington, Pub. No. 361, Contrib. to Embryol., 1925, xvi, 125.
32. Forkner, C. E.: Clinical and pathologic differentiation of the acute leukemias, with special reference to acute monocytic leukemia, Arch. Int. Med., 1934, liii, 1–34.
33. Arneth, J.: Die neutrophilenweissen Blutkörperchen bei Infektionskrankheiten, 1904, Gustav Fischer, Jena.
34. Schilling, V.: Über die Notwendigkeit grundsätzlicher Beachtung der neutrophilen Kernverschiebung im Leukozytenbilde und über praktische Erfolge dieser Methode, Ztschr. f. klin. Med., 1920, lxxxix, 1–41.
35. Wiseman, B. K., and Doan, C. A.: The lymphatic reaction in tuberculosis, Am. Rev. Tuberc., 1934, xxx, 33–59.
36. Anderson, R. J.: Chemistry of lipoids of tubercle bacilli, Physiol. Rev., 1932, xii, 166–189.
37. Meleney, H. E.: Histopathology of kala-azar in hamster, monkey and man, Am. Jr. Path., 1925, i, 147–168.
38. Doan, C. A., and Zerfas, L. G.: Rhythmic range of white blood cells in human, pathological leukopenic and leukocytic states, with study of 32 human bone marrows, Jr. Exper. Med., 1927, xlvi, 511–539.
39. Sabin, F. R.: Studies of living human blood cells, Bull. Johns Hopkins Hosp., 1923, xxxiv, 277–288.
40. Murray, E. G. D., Webb, R. A., and Swann, M. B. R.: Disease of rabbits characterized by a large mononuclear leukocytosis, caused by hitherto undescribed bacillus, *Bacterium monocytogenes*, Jr. Path. and Bact., 1926, ccxciii, 407–439.
Webb, R. A., and Witts, L. J.: Monocytes of rabbit in *B. monocytogenes* infection; study of their staining reactions and histogenesis, Jr. Path. and Bact., 1927, xxx, 687–712.
41. Fraenkel, A.: Über acute Leukamie, Deutsch. med. Wchnschr., 1895, xxi, 639.
42. Naegeli, O.: Über rotes Knochenmark und Myeloblasten, Deutsch. med. Wchnschr., 1900, xxvi, 287–290.
43. Downey, H.: Myeloblast, its occurrence under normal and pathological conditions, and its relations to lymphocytes and other blood cells, Folia haemat., 1927, xxxiv, 65, 145.
44. Sabin, F. R., Austrian, C. R., Cunningham, R. S., and Doan, C. A.: Studies on maturation of myeloblasts into myelocytes and on amitotic cell division in peripheral blood in subacute myeloblastic leukemia, Jr. Exper. Med., 1924, xl, 845–871.
45. Simpson, M. E., and Deming, J. M.: Identification of myeloblasts with vital stains, Folia haemat., 1927, xxxiv, 103–124.
46. Dameshek, W.: Acute monocytic (histiocytic) leukemia, Arch. Int. Med., 1930, xlvi, 718–740.
47. Clough, P. W.: Monocytic leukemia, Johns Hopkins Hosp. Bull., 1932, li, 148–177.
48. Gittens, R., and Hawksley, J. C.: Reticulo-endotheliomatosis, ovarian endothelioma and monocytic (histiocytic) leukemia, Jr. Path. and Bact., 1933, xxxvi, 115–131.
49. Orr, J. W.: Monocytic leukemia, Lancet, 1933, i, 403–407.
50. Lawrence, J. S., Josey, A. I., and Young, M. W.: Monocytic leukemia—report of three cases, Folia haemat., 1931, xliv, 332–351.
51. Böhne, C., and Huismans, L.: Beiträge zur Kenntnis der chronischen leukämischen Reticuloendotheliosen, Virchow's Arch. f. path. Anat., 1932, cclxxxiii, 575–592.
52. Marchal, G., and Bargeton, A.: Difficultés de diagnostic entre maladie de Hodgkin et leucémie à monocytes, Sang, 1933, vii, 321–327.

53. Fleischmann, P.: Der zweite Fall von Monozytenleukämie, Folia haemat. (Archiv.), 1916, xx, 17–33.
54. Schwirtschewskaja, B.: Über leukämische Reticuloendotheliose, Virchow's Arch., 1928, cclxvii, 456–476.
55. Vyshegorodtzewa, V. D.: Zur Frage der monozytären Leukämie, Folia haemat., 1929, xxxviii, 355–366.
56. Farley, D. L.: Monocytic leukemia, Med. Clin. N. Am., 1930, xiii, 991–999.
57. Barton, R. B.: Endothelioid cell in acute leukemia, Jr. Lab. and Clin. Med., 1927, xii, 855–857.
58. Ugriumow, B.: Ein Fall von akuter Reticulo-Endotheliose, Centralbl. f. allg. Path. u. path. Anat., 1928, xlii, 103–106.
59. Bykowa, O.: Das reticulo-endotheliale System in der Pathogenese der akuten Leukosen, Folia haemat., 1931, xliii, 475–485.
60. Hittmair, A.: Zur Frage der sog. Retikuloendotheliosen, Folia haemat., 1928, xxxvii, 321–376.
61. Bock, H. E., and Wiede, K.: Zur Frage der leukämischen Retikuloendotheliosen (Monocytenleukämien), Virchow's Arch. f. path. Anat., 1930, cclxxvi, 553–586.
62. Sternberg, C.: Über Leukosarkomatose, Wien. klin. Wchnschr., 1908, xxi, 475–480.
63. Bingel, A.: Monozytenleukämie (?), Deutsch. med. Wchnschr., 1916, xlii, 1503–1505.
64. Sydenstricker, V. P., and Phinizy, T. B.: Acute monocytic leukemia. Case with partial autopsy, Am. Jr. Med. Sci., 1932, clxxxiv, 770–777.
65. Payenneville, J., and Cailliau, F.: Étude d'un cas de leucémie cutanée de forme mixte avec généralisation secondaire et syndrome leucémique aigu terminal, Ann. de dermat. et syph., 1930, i, 844–866.
66. Lasowsky, J. M.: Über eine Systembezogene blastomartige Hyperplasie des Reticuloendotheliums (sog. Reticuloendotheliom), Virchow's Arch. f. path. Anat., 1933, cclxxxviii, 631–640.
67. Marchal, G., Soulié and Mahoudeau-Campoyer: Sur un cas de leucémoïde à monocytes, Sang, 1933, vii, 199–204.
68. Bykowa, O.: Retikulo-endotheliale Leukosen (mit Affection der Haut), Folia haemat., 1933, li, 96–104.
69. Foord, A. G., Parsons, L., and Butt, E. M.: Leukemic reticuloendotheliosis (monocytic leukemia), Jr. Am. Med. Assoc., 1933, ci, 1859–1866.
70. Doan, C. A.: Neutropenic state; its significance and therapeutic rationale, Jr. Am. Med. Assoc., 1932, xcix, 194–202.
71. Pick, L.: Niemann-Pick's disease and other forms of so-called xanthomatosis, Am. Jr. Med. Sci., 1933, clxxxv, 601–616.
72. Bloom, W.: Histogenesis of essential lipoid histiocytosis (Niemann-Pick's disease), Arch. Path., 1928, vi, 827–859.
73. Epstein, E., and Lorenz, K.: Die Phosphatidzellverfettung der Milz bei Niemann-Pickscher Krankheit verglichen mit der Lipoidchemie des Morbus Gaucher und der Schüller-Christianschen Krankheit, Ztschr. f. physiol. Chem., 1930, cxcii, 145–170.
74. Pick, L.: Classification of diseases of lipoid metabolism and Gaucher's disease, Am. Jr. Med. Sci., 1933, clxxxv, 453–469.
75. L'Esperance, E. S.: Experimental inoculation of chickens with Hodgkin's nodes, Jr. Immunol., 1929, xvi, 37–60.
76. Stewart, F. W., and Doan, C. A.: Analysis of lymphadenopathy question with special reference to Hodgkin's disease and tuberculosis, Ann. Surg., 1931, xciii, 141–152.
77. Dameshek, W.: Proliferative diseases of reticulo-endothelial system; aleukemic reticulosis, Folia haemat., 1933, xlix, 64–85.

REMARKS ON THE DIAGNOSIS OF CORONARY OCCLUSION *

By Louis Hamman, M.D., F.A.C.P., *Baltimore, Maryland*

About eight or ten years ago, at a time when I was much interested in the clinical manifestations of coronary occlusion, I was often asked to see patients with symptoms of collapse following a severe attack of pain in the chest and under these circumstances had the satisfaction of pointing out how clearly and simply the diagnosis of coronary occlusion could be made. However, these opportunities have come very, very rarely during the past few years. At the present day the humblest practitioner of medicine and the most recent graduate are so thoroughly familiar with the clinical picture of this tragic event and so acutely alive to its recognition that the opinion of a consultant is seldom needed to suggest the diagnosis. Indeed, the diagnosis is frequently and readily proposed and having passed through the earlier period when it was seldom even thought of, I am now often surprised by being asked to see patients with coronary occlusion who are really suffering from some other disorder. It is astonishing how rapidly information about the condition has spread through the profession and with what eagerness and enthusiasm the knowledge has been applied. Now, when almost every sudden, severe pain in the chest of a person past middle life is at once called coronary occlusion, seems the appropriate time to sound a warning. There are other diseases of the heart, lungs and abdominal organs which may so closely resemble coronary occlusion that they are often distinguishable from it only with great difficulty and sometimes not until autopsy discloses the real state of affairs. It is not my purpose to discuss in detail the differential diagnosis of coronary occlusion. I wish only to dwell upon five conditions which in my experience have occasionally been confused with it. These conditions are upper abdominal disease, pericarditis, pulmonary embolism, rupture of the aorta and interstitial emphysema of the lungs.

I. Upper Abdominal Disease

The diagnostic difficulty of distinguishing between coronary occlusion and upper abdominal disease is often very great. In spite of the fact that the similarity between the two conditions is generally well known the difficulty arises again and again. Sometimes the course of events quickly dispels uncertainty but at other times it is almost impossible to make a confident decision. The matter has been so often and so widely discussed that no more is necessary than briefly to mention it. On four occasions the difficulty has greatly puzzled me.

On one, the patient was operated upon for what was thought to be a perforated peptic ulcer. The peritoneal cavity and abdominal organs were

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

found to be normal. Later a period of auricular fibrillation, the transient appearance of a pericardial friction rub and the occurrence of pulmonary embolism established the correct diagnosis.

On another, gall-stone colic with infection of the bile passages and gall-bladder was accepted as the explanation for pain, fever, leukocytosis and a slightly swollen, tender liver. Only weeks later was the error corrected when the unmistakable signs of beginning myocardial insufficiency appeared.

On still another, a prominent surgeon, called to see a man with intense upper abdominal pain, decided the symptoms were due to coronary occlusion not to gall-stones and asked a physician to take charge of the situation. However, two days later the patient was deeply jaundiced.

On the fourth, surgeons and physicians argued pro and con for two days, when finally the characteristic symptoms of coronary occlusion appeared.

II. Pericarditis

Pericarditis may come on with sudden severe pain and the pain be quickly followed by the symptoms of myocardial insufficiency. Under these circumstances the severe pain, the pericardial friction, the fever and leukocytosis, the shortness of breath, the cyanosis, the congestive failure may simulate the manifestations of coronary occlusion. Again and again this diagnosis is made when patients with pericarditis are first brought into the hospital. On two occasions I have been consulted by young men under 40 who have told me that a diagnosis of coronary occlusion had been made a year or two before on the evidence of severe pain coming on abruptly and accompanied by a pericardial friction, fever, shortness of breath and certain abnormalities in the electrocardiogram. After recovery from this illness they had remained perfectly well and had had no symptoms whatsoever referable to the circulatory system. The examination at the time of their visit to me failed to disclose the slightest sign of any abnormality about the heart or circulation. I cannot cease wondering if they may have had pericarditis and not coronary occlusion. I add a brief summary of a few illustrative cases.

Case I

A colored laborer, 29 years of age, entered The Johns Hopkins Hospital on June 15, 1933, complaining of severe pain over the heart. For a number of years he had been very obese, weighing as much as 240 pounds. The gain in weight had come on rather quickly about seven years before. During a year and a half before his admission to the hospital he had been treated in the Orthopedic Clinic for genu valgus and flat feet.

At four o'clock on the afternoon of the day before his admission the patient was awakened from a nap by excruciating pain beneath the upper end of the sternum. He sat upon the edge of the bed gasping for breath and moaning with pain. His misery continued unabated during that night and during the whole of the next day. In the evening he was persuaded to enter the hospital.

Examination: Temperature 102° F.; pulse 120; respirations 48; blood pressure 112 systolic and 50 diastolic.

The patient was an obese young colored man. He lay propped up in bed with a moderate amount of dyspnea, complaining of intense pain over the heart. The least movement greatly increased the pain. Breathing was rapid and shallow. Obviously he was very ill. There was no cyanosis, no cough. The eyes were normally prominent. The pupils were equal and reacted actively. The eye movements were normal. The fundi showed no noteworthy abnormality. The nasal septum was perforated. The teeth were in very poor condition and there was marked pyorrhea. The tonsils were large and small patches of white exudate were seen on the left tonsil. The glands at the angle of the jaw were palpable, otherwise there was no glandular enlargement. The thyroid was normal in size. The trachea was in the midline; there was no tracheal tug. The chest was well formed and symmetrical. Over the bases of both lungs there were dullness, diminution in the intensity of the breath sounds and many moist râles. These signs were more marked on the left side than on the right except that the râles were much more numerous on the right. Over the heart there was a faint rippling pulsation in the fourth and fifth interspaces. The apex beat could not be seen or felt. The area of cardiac dullness was greatly enlarged and had a somewhat globular contour. Dullness extended 5 cm. to the right and 12 cm. to the left of the midline. The sounds were distant and faint. A soft systolic murmur was heard at the apex. The second pulmonic sound was accentuated. There was gallop rhythm. A loud to-and-fro pericardial friction was heard all over the heart. The pulse was regular, soft, not paradoxical. The peripheral vessels were not thickened. The abdomen was prominent and obese. Examination of the abdomen was difficult with the patient in a sitting position. There was no ascites. The liver seemed to be somewhat enlarged, the edge indefinitely felt 3 cm. below the costal margin. There was minimal pitting edema over the shins. The neurological examination was negative.

Course in the Hospital: The patient was desperately ill on admission and although from time to time there seemed to be a little improvement in his condition, the course was downhill. He died on the twelfth day after entering the hospital. During this period he always was very drowsy. He complained little but always had pain over the heart which was much increased by breathing and by changing posture. The area of cardiac dullness steadily increased so that at the time of death it was much larger than when he entered the hospital, the area measuring 6 cm. to the right and 16 cm. to the left of the midline. How much of the dullness was due to enlargement of the heart and how much to pericardial thickening and effusion it was impossible to say. There never was more than the slightest edema. The liver was not greatly enlarged, extending only a little below the costal margin. The lung signs increased in extent. At first there were the signs of fluid in both pleural cavities, later there seemed to be in addition evidence of consolidation particularly in the right lower lobe. Four attempts were made to tap the pericardium from different positions. The attempts made over the heart all failed to yield fluid. Two punctures in the left axillary area yielded a small amount of fluid, on each occasion about 150 c.c. However, one could not be certain that this fluid came from the pericardial sac because there was fluid in the left pleural cavity. The fluid from the first successful tap was hemorrhagic, the cell count being: red blood corpuscles 300,000, leukocytes 770. The second successful tap gave a turbid, yellow fluid of specific gravity 1.021, containing 10 grams of albumin per liter. The cell count was red blood cells 220,000, leukocytes 3200. A differential count of the leukocytes showed 62 per cent polymorphonuclears, 35 per cent lymphocytes and 3 per cent monocytes. The right pleural cavity was tapped on June 21 and 50 c.c. of fluid were removed. The patient finally became very weak with extraordinarily rapid, panting breathing and on June 27 he was found dead in

bed. On admission the pulse was rapid and regular, later it was rapid and totally irregular, and shortly before death it again became regular.

In this patient the sudden severe pain followed at once by the symptoms of myocardial insufficiency aroused the suspicion that he might have coronary occlusion or rupture of the aorta with the formation of a dissecting aneurysm. After a few days of observation it was apparent that he had pericarditis. On the wards it was thought that he had tuberculous pericarditis, but autopsy demonstrated that it was rheumatic.

The anatomical diagnosis reads as follows: Rheumatic vegetations on mitral and aortic valves; rheumatic scarring of mitral, aortic and tricuspid valves; scarring of myocardium; cardiac hypertrophy; acute rheumatic pericarditis; bilateral sero-fibrinous pleurisy; pulmonary edema; thrombosis of a branch of the pulmonary artery, right upper lobe; slight lobular pneumonia; chronic passive congestion of lungs and liver; acute splenic tumor; diffuse scarring of pancreas and testes; beginning arteriosclerosis; obesity.

Case II

A colored laborer, then 37 years of age, came to the Medical Clinic of the Out-Patient Department of The Johns Hopkins Hospital on December 8, 1926, complaining of a cold which he had had for a week. The physical examination on that occasion showed no important abnormality. The heart was normal in size, the sounds perfectly clear. The impression was expressed that the patient had an acute upper respiratory infection. A roentgenogram of the chest showed the lungs to be clear. The Wassermann reaction on the blood serum was strongly positive, and the patient was referred to the Syphilis Clinic for treatment. He was reëxamined in that department a few days later and once more the lungs and heart were found to be normal.

On June 8, 1933, the patient entered the hospital complaining of pain in the chest which had come on the previous day. He was in the hospital for one month with a characteristic mild attack of lobar pneumonia involving the left lower lobe and due to the pneumococcus Type IV. Throughout the period of his stay in the hospital the heart was totally irregular. He had been a patient at Mercy Hospital in December 1932. A letter from that hospital states that he had had lobar pneumonia of the left lower lobe. At that time also the heart was fibrillating. The cause for the auricular fibrillation gave rise to much speculation. Some thought that in spite of the fact that the heart was little if any enlarged and the sounds perfectly clear, that he might have rheumatic mitral valve disease. However, opinions favored the view that the disturbance of rhythm was associated with arteriosclerotic heart disease.

The patient was admitted to the hospital again on January 2, 1934. After his discharge on July 8, 1933, he was reasonably well but he did not feel as well as he had before. He came to the Syphilis Clinic from time to time where he was treated for the luetic infection. Off and on he worked at odd jobs but felt unable to work regularly. There was some shortness of breath on exertion. During this period physical examination and roentgenograms demonstrated the persistence of infection in the lower lobe of the left lung. One week before the second admission to the hospital, while working in the market moving heavy barrels, he was suddenly taken with severe pain in the interscapular area. The pain was so intense that he had to stop work and go home. He began to cough; the cough was worse at night and he was unable to sleep on account of the severity of the pain. He grew more and more short of breath. Two days before entering the hospital the pain shifted from the back to the front of the chest and was particularly severe over the lower end of the sternum. The pain, he said, was exceedingly sharp, as severe as a toothache.

Examination: Temperature 100.2° F.; pulse 104; respirations 24; blood pressure 108 systolic and 54 diastolic.

The patient was propped up in bed complaining of severe pain about the heart. He was a short man, a typical chondrodystrophic dwarf. His pain seemed to be quite severe. There was only a moderate degree of dyspnea. Over the left shoulder was the scar of a stab wound received years before. The eyes were normally prominent. The pupils were a little irregular and constricted due to the administration of morphia. Later examinations demonstrated that they reacted actively to light and on accommodation. The eye movements were normal. The fundi showed a moderate degree of arteriosclerosis. In the left eye there was partial detachment of the retina. Many teeth had been extracted; those remaining were in poor condition. The throat showed nothing remarkable. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. Over the lower lobe of the left lung the percussion note was impaired, the breath sounds were enfeebled, and a small number of scattered râles were heard after cough. The heart was enlarged. Cardiac dullness measured 5 cm. to the right and 12 cm. to the left of the midline. The apex beat was easily felt. The heart sounds were clear, the second pulmonic louder than the second aortic. A loud pericardial friction rub was heard over the heart, loudest in the fourth interspace. The area of dullness over the manubrium was somewhat increased. The rhythm was totally irregular. The peripheral vessels showed a moderate degree of arteriosclerosis. The abdomen was normal in appearance. No masses were felt. The liver and spleen were not enlarged. The genitalia showed nothing abnormal. There was no edema. The neurological examination was negative.

In this patient the situation was confusing. He had been fibrillating for over a year and it was assumed that he had arteriosclerotic heart disease. The sudden onset of pain followed by fever, leukocytosis, the symptoms of myocardial insufficiency and a pericardial friction suggested that he might have coronary occlusion. After a few days the signs of pericardial effusion developed and aspiration yielded a purulent fluid from which pneumococcus Type IV was cultivated. The pericardial sac was opened and drained. For a while the patient improved but later grew worse again and died two months after entering the hospital.

The anatomical diagnosis reads: History of pneumonia followed by pericarditis; dense pleural adhesions, left lower lobe; adherent thickened pericardium with drained, walled-off pericarditis; mycotic aneurysm of arch of aorta extending into pericardium; generalized pleural adhesions; hypertrophy of right ventricle; chronic passive congestion of viscera; thrombosis in old caseous primary focus, right lower lobe; encapsulated caseous area in peribronchial nodes.

In both of these patients a very loud pericardial friction was heard over the whole heart. This is precisely what is usually heard with pericarditis and it is an important point distinguishing it from coronary occlusion. When a pericardial friction appears over an infarcted area of heart muscle it is a faint rub often difficult to hear, well localized and transient. I have never heard a diffuse, loud friction with coronary occlusion.

III. Pulmonary Embolism

In 1927 I published an article calling attention to the very great importance of embolic phenomena in the diagnosis of coronary occlusion.

I pointed out that pulmonary embolism occurred frequently and cited an instance illustrating how very, very difficult it may be to distinguish between coronary occlusion and pulmonary embolism. On account of its great interest in this connection I report the case again.

CASE III

A woman, 69 years of age, was operated upon by Dr. E. H. Richardson at the Hospital for the Women of Maryland and a perineal repair performed. She had been carefully examined a few weeks before by Dr. H. M. Thomas, Jr., who found no important abnormality, except that the blood pressure was systolic 160 mm. Hg and diastolic 80 mm. Hg. After the operation, convalescence progressed uneventfully, and on the twelfth day the patient was out of bed. On the evening of the fifteenth day, while walking about the corridor, she suddenly had a feeling of faintness and would have fallen had she not been supported by a nurse. When she had been gotten to bed she complained of a feeling of pressure over the chest and difficulty in getting her breath. The following morning she still complained of constriction in the chest and shortness of breath.

The blood pressure was much lower than it had been before operation, but no estimate had been made after operation. The pulse rate, previously around 80, rose to 100 and over and remained thereabout. The heart was a little further out to the left. The patient had a grayish, slightly cyanotic color, was deeply prostrated, and gave one the impression of being seriously ill. The following afternoon a definite coarse, to-and-fro pericardial friction was heard over the sternum and to the left of it, which disappeared after six or eight hours and did not return. The lungs remained clear except for a few râles at the base, and there was no cough and no bloody expectoration.

For a week or longer the patient remained prostrated, was delirious and displayed Cheyne-Stokes breathing. On the twenty-seventh day after operation, swelling of the left leg with pain in the groin pointed clearly to thrombosis of the left femoral vein. The swelling of the leg subsided, the delirium cleared, the pulse slowed and the patient gradually improved. In September she was out of bed and she left the hospital September 24 in good condition.

At the time I thought the patient had had coronary occlusion but even then I was perplexed and uncertain, as shown by the comments I added: "It was my own belief, shared by Dr. Thomas, that the patient had had a coronary occlusion. The character of the attack, the appearance of the patient, the rapid pulse, the fall in blood pressure, the pericardial friction together make a convincing picture. Hearing about the illness without an opportunity to see the patient, one might well argue for pulmonary embolism. The time after the operation, the sudden onset, the symptoms of shock, the left femoral thrombosis, all strongly suggest pulmonary embolism. It might even be suggested that the rub heard over the heart may have been a pleuro-pericardial friction. I am convinced it was not. However, it is not my intention to argue the point but rather to illustrate how difficult at times the diagnosis may be."

It is certainly true that the symptoms and the course of events during the illness were typically characteristic of postoperative thrombophlebitis with pulmonary embolism and no other diagnosis would have been considered

had it not been for the presence of a pericardial friction. Does the appearance of a pericardial friction make it necessary to abandon the diagnosis of pulmonary embolism with infarction when all the other symptoms are typical of the condition? This question troubled me continuously until the observation of a second somewhat similar instance convinced me that a loud pericardial friction may occur with infarction of the lower lobe of the left lung under circumstances when the possibility of the occurrence of coronary occlusion is very remote, if not indeed beyond all reasonable expectation.

I shall not now pause to discuss whether the pericardial friction was an endopericardial or an extrapericardial rub. It seems to me likely that it was extrapericardial. All I can say with certainty is that it was a very loud to-and-fro friction and that from the character of the sounds it was impossible to decide whether it was endo- or extrapericardial. The main facts about this second case are as follows:

Case IV

A clergyman, 43 years of age, entered the Bon Secours Hospital under the care of Dr. E. D. Freeman, on May 5, 1932. During the previous year and a half he had had recurring attacks of severe upper abdominal pain which Dr. Freeman diagnosed gall-stone colic. Under conservative treatment there was no improvement, indeed, the attacks became more frequent and more severe. The patient was a rather obese man, in good general condition, who showed no abnormality on physical examination other than tenderness in the epigastrium and in the gall-bladder area. The blood pressure was 132 systolic and 78 diastolic. On May 19, 1932, the patient was operated upon by Dr. E. H. Hayward and the gall-bladder removed. The diagnosis made at operation was chronic perforation of the gall-bladder, chronic cholecystitis and hepatitis adjacent to the gall-bladder. Dr. H. S. Everett examined the tissues removed at operation and reported subacute cholecystitis and cholelithiasis.

During the first week after operation the patient progressed satisfactorily. From time to time he had a little asthmatic wheezing. He had had asthma since 16 years of age, particularly in the spring and early fall. Everything went well until the morning of May 25 when he was suddenly taken with severe pain in the left axilla and left shoulder. The temperature which during the previous week had fluctuated between 98° and 100° rose to 102° and the pulse rate to 120. Later on the same day a pleural friction rub was heard in the left axillary area. The patient was somewhat shocked and a little cyanotic. The following four or five days he had cough with frankly bloody expectoration. The symptoms were very characteristic of pulmonary embolism and this diagnosis was made. The patient then steadily improved during the week until June 2. On that day when turning on the left side, he suddenly went into a condition of collapse. There was great shortness of breath, he became pale and cyanotic and the pulse rate rose to 130. The following morning a loud to-and-fro friction was heard all over the heart. The manifestations on this occasion, though somewhat more severe, were exactly like those which had occurred a week before, except that there was no pain and the symptoms of collapse were followed by the appearance of a loud pericardial friction. The presence of the precordial friction led to the suspicion that this attack might be one of coronary occlusion. With this diagnosis in mind, Dr. Freeman asked me to see the patient.

At the time of my visit, which was about 32 hours after the onset of the symptoms of collapse, the patient still was very ill; he was propped up in bed quite dyspneic, very pale, somewhat cyanotic and sweating profusely. It was impossible

to make a thorough examination. However, there were definite signs of consolidation in the left axilla and in this area also a pleural friction. All over the heart there was a loud grating to-and-fro friction. There was no variation in the intensity of the rub with respiration. The pulse was rapid, of small excursion and the pressure was low.

From then on the patient steadily improved. At the end of four days the pericardial rub had disappeared and after that he made a slow but otherwise uneventful recovery. He left the hospital on July 5, 1932.

After leaving the hospital when he began to walk about he noticed that there was some swelling of the left calf; the left calf measured two or three centimeters more than the right calf. He wore a pressure bandage and the swelling soon disappeared.

On March 3, 1934, I had an opportunity to examine the patient again. He said he had been perfectly well since leaving the hospital and had had no symptoms except a little irritation in the throat and a little wheezy cough from time to time. These asthmatic symptoms, however, had been much less severe than they had been in former years. There had been no symptoms whatsoever referable to the heart or circulation. No pain about the heart, no palpitation, no shortness of breath, no symptoms which might to the slightest degree suggest angina pectoris. The examination on this occasion was entirely negative except that the patient had gained some weight and was moderately obese. The notes of the examination are as follows:

Examination: Temperature 98.2° F.; pulse 72; respirations 16; blood pressure 132 systolic and 80 diastolic. Weight 188 pounds. Height 5 ft. 7¾ inches.

The patient is somewhat obese, 32 pounds above the average weight for his height and age. He has a good color and a healthy appearance. He is a mouth-breather. The eyes are normally prominent, pupils equal, react actively, eye movements are all normal. The teeth are in good condition. The tongue is clean. The throat shows no abnormality. There is no enlargement of the superficial lymph nodes. The thyroid is just felt, average size, symmetrical, no nodules. The chest is well formed and symmetrical, with a wide costal angle. Movements are equal on the two sides. The lungs are perfectly clear except for a slight degree of emphysema. The apex beat of the heart is a barely visible impulse in the fifth interspace inside the nipple line. The area of cardiac dullness is not enlarged. There is no impairment over the manubrium. Heart sounds are clear and of normal quality. Pulse is regular; the peripheral vessels not thickened. The abdomen is normal in appearance. In the right upper quadrant is the scar of the operation wound. There is a fairly thick panniculus. No tenderness. No masses are felt. The liver and spleen are not enlarged. There is a little prominence of some of the superficial veins about the left ankle. At the present time no swelling of the left leg. The measurements about the calves are 38 cm. on each leg.

IV. Rupture of the Aorta

When this Society met at Baltimore two years ago I demonstrated at Ward Rounds a patient showing all of the classical manifestations of coronary occlusion. The following day a distinguished Visiting Physician selected the patient to illustrate his remarks upon the same subject. At the time no one doubted the accuracy of the diagnosis. I shall briefly state the main facts about the case and tell the subsequent developments.

Case V

A white married housewife, 63 years of age, was admitted to The Johns Hopkins Hospital on November 27, 1930, complaining of intense pain under the sternum and

shortness of breath. For four or five years she had had dyspnea on exertion and occasionally a feeling of substernal pressure with dyspnea which would pass after a short period of rest. Two days before admission, while varnishing a piece of furniture, she suddenly was seized with intense pain in the region of the heart. She described this sensation saying it felt "as though the insides were being torn out" again "as though there were an expanding ball inside the chest about to burst," and yet again "as though she had been hit by a sledge hammer." She fell back dazed, perhaps even unconscious, and was carried to bed. The pain continued, not so severe as at first, but still very severe, and a hypodermic injection administered by a physician gave but little relief. She vomited a number of times and had some cough with slightly blood-streaked expectoration. She was brought to the hospital 53 hours after the onset of symptoms.

Examination: Temperature 102° F.; pulse 108; respirations 34; blood pressure 210 systolic and 140 diastolic.

The patient was a rather obese woman, highly flushed, breathing rapidly and complaining of substernal pain. There was moderate cyanosis. The eyes were normally prominent, pupils equal, reacted actively. The eye grounds showed moderate arteriosclerotic changes. The teeth had been extracted and she wore a complete double denture. No enlargement of the superficial lymph nodes. The thyroid was not enlarged. The lungs showed no abnormality other than the presence of numerous moist râles over both lower lobes. The heart was enlarged, sounds much enfeebled. There was a faint systolic murmur at the apex. The sounds at the base could scarcely be heard. The pulse was regular except for an occasional extrasystole. The abdomen was soft and relaxed. No tenderness. Liver and spleen not enlarged. Slight pitting edema over the shins. The pelvic and rectal examinations revealed nothing abnormal.

Course During First Stay in the Hospital: The patient was given morphia, was then bled and digitalis started. She continued to have severe attacks of substernal pain. The blood pressure, which on admission was 210 systolic and 140 diastolic, fell rapidly to 110 systolic and 78 diastolic then slowly rose again during the following twelve hours to 180 systolic and 70 diastolic. The temperature was 99° the following day and thereafter only occasionally a little elevated. The leukocytes varied from 9,000 to 16,000 during the first week. The patient's general condition, which was desperate on admission, improved a little but she continued to be miserable, with frequent attacks of substernal pain and severe attacks of coughing associated with urgent dyspnea. The pulse, regular on admission, was totally irregular the following day and fibrillation continued from that time. Paravertebral injections of the sympathetic rami somewhat relieved the pain but did not abolish it. The physical examination showed but little change during the period of her stay in the hospital. The heart sounds became more forcible. There was a great deal of discussion about a diastolic murmur, which some heard but which others could not hear. Sometimes this murmur was heard only at the apex, at other times faintly to the left of the sternum. The patient left the hospital April 15, 1931, still in a rather miserable and unsatisfactory state.

Interval Note: At home she was always miserable. She could make no effort and only with assistance could take a few steps from chair to chair. On July 6, 1931, she was seen in the Dispensary when she was very short of breath and cyanotic. Examination otherwise did not differ from what had been found when she was in the hospital. Later in July she began to have still more severe attacks of pain and the cough became more troublesome. In October she began to have a different type of pain from that which she had had before. This consisted of attacks of severe, sharp pain in the epigastrium, and from then on this symptom remained more prominent than any other. Patient was admitted to the hospital again on November 20, 1931.

Examination: Temperature 99.4° F.; pulse 88; respirations 26; blood pressure 150 systolic and 95 diastolic.

The patient was propped up in bed, with marked dyspnea. Evidently she had lost a great deal of weight. There was moderate cyanosis. She complained bitterly of severe pain about the heart and gnawing pain in the epigastrium. Occasional attacks of cough occurred with severe dyspnea. The face was quite drawn and contracted with pain. Skin and mucous membranes had a fairly good color. The eyes showed nothing abnormal. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. The lungs were clear except for numerous moist râles over both lower lobes and a few scattered sonorous râles. The heart was enlarged, the area of dullness measuring 5 cm. to the right and 12 cm. to left of the midline. At the apex the first sound was loud and booming and was followed by a loud, blowing systolic murmur. In the aortic area there was a rough systolic murmur, and the aortic second sound was accentuated and somewhat ringing in quality. The pulse was totally irregular; peripheral vessels thickened and tortuous. The abdomen was soft and relaxed. Marked tenderness was present in the epigastrium, particularly over the aorta. The aorta could easily be felt. It seemed to be wider than normal and to pulsate violently. No clubbing of the fingers was noted and no edema of the legs. The neurological examination was negative.

Course: After admission the patient improved very little. She was constantly most miserable, with substernal pain, attacks of coughing with intense dyspnea, and complaining always of a severe gnawing pain in the epigastrium which varied a good deal in intensity. In some of the attacks of dyspnea there was wheezing. Everyone agreed that the abdominal aorta was dilated and tender and some thought there was a fusiform dilatation. On this admission, as on the first, there was a dispute about a diastolic murmur. At times the patient was delirious. On February 22 she contracted the respiratory infection then prevalent on the Ward. She developed bronchopneumonia and on February 27, 1932, was released by death from all her misery and suffering.

The blood count demonstrated a mild secondary anemia. The Wassermann reaction on the blood serum was negative. The urine contained albumin and a few casts. The temperature on the first admission was 102°; it fell rapidly to normal and thereafter varied at first from 97° to 99°, occasionally going to 100°. During the second admission it varied from 97.6° to 100°. Later it fell to normal and with the terminal pneumonia rose and varied from 99.6° to 104°.

Many electrocardiograms were taken. In all there was evidence of myocardial disease but the curves did not show the changes characteristic of coronary occlusion.

Roentgenograms showed enlargement of the heart and aorta. The measurements of the teleroentgenogram were M.R. 6, M.L. 10.4, T. 27.2.

The anatomical diagnosis reads: Arterio- and arteriolosclerosis; scarring of kidneys; atrophy of acinar tissues of pancreas; history of hypertension and auricular fibrillation; cardiac hypertrophy and dilatation; focal necroses and scars in myocardium; chronic passive congestion of viscera; bilateral hydrothorax; subcutaneous edema; dissecting aneurysm of aorta and iliac arteries; saccular aneurysm of dissecting aneurysm; fibrous adhesions between right auricle, arch of the aorta and pericardium; chronic bronchitis and tracheitis; emphysema; lobular pneumonia; chronic cervicitis and retention cysts in uterus; myomata and polypi uteri; secondary anemia; hyperplasia of bone-marrow.

During the past three years I have encountered seven instances of rupture of the aorta at clinical pathological conferences. In all seven the diagnosis of coronary occlusion had been made when the patient first entered the hospital but in five it was changed to rupture of the aorta before

the autopsy findings were disclosed. When the patient dies shortly after the accident occurs the distinction between the two may be very difficult as the following case illustrates:

Case VI

A white man, 79 years of age, was brought to The Johns Hopkins Hospital on November 12, 1929, in an unconscious state. He had always been in remarkably good health except that for some time he had been somewhat short of breath on exertion and occasionally had had a little substernal pain especially at night. About 10 o'clock on the morning of November 12 as he was riding home from work on the street car, he was suddenly seized with severe pain under the sternum. He became very dizzy and lost consciousness. He was picked up by the police and brought to the hospital. In the accident room he regained consciousness and could only state that he had had a very severe pain and had then lost consciousness. He was obviously deeply shocked and quite ill. He was a little short of breath, the hands and feet were cold, there was marked cyanosis and the pulse was imperceptible. The blood pressure could not be taken by auscultation; by palpation the systolic pressure was 58 mm. Hg. He was at once admitted to the Ward.

Examination: Temperature 98.7° F.; pulse 76; respirations 24.

The patient was an old man with marked arteriosclerosis of the peripheral and retinal vessels. Respirations were somewhat labored. He complained of a dull aching under the sternum. The chest was narrow and thin, disproportionately wide antero-posteriorly. The lungs showed nothing remarkable except a few râles at the bases. The heart was somewhat enlarged, the area of dullness measuring 4 cm. to the right and 11½ cm. to the left of the midline. The apex impulse was in the seventh interspace; the action irregular due to the occurrence of numerous extrasystoles. The first sound at the apex was followed by a short systolic murmur. The sounds were feeble and could not be heard at the base. The abdomen showed nothing remarkable except that the liver was felt 5 cm. below the costal margin.

Course in the Hospital: After stimulation, the patient's condition at first improved somewhat. The blood pressure in the right arm rose to 174 systolic and 130 diastolic. The pulse was never more than vaguely perceptible. Following the accident he remained anuric for 30 hours.

Two days after admission he suddenly developed abdominal distention, complained of abdominal pain and soon afterward died, apparently of cardiac failure. Shortly before death there was a little dullness at the right base suggesting the presence of a patch of pneumonia.

Laboratory Examinations: Blood count: Hemoglobin 74 per cent; red blood corpuscles 3,740,000; leukocytes 11,560.

The leukocytes varied from 12,000 to 18,000. The Wassermann reaction on the blood serum was negative. The urine showed an abundance of albumin with many hyaline and granular casts. The nonprotein nitrogen and uric acid of the blood were at a normal level. The temperature on admission was normal and then gradually rose, varying irregularly between 99° and 101°.

Roentgenogram of the chest showed a soft infiltration at both apices, tuberculous in character. Electrocardiogram; rate approximately 94. Rhythm totally irregular. Slurring of R-waves in all leads, low voltage in all leads.

The anatomical diagnosis reads: Dissecting aneurysm of ascending aorta with rupture into pericardium; hemopericardium; arteriosclerosis; emphysema; bilateral multilocular hydrocele; thickening of splenic capsule; diverticulum of duodenum; minute abscess of liver.

In distinguishing between coronary occlusion and rupture of the aorta too much reliance must not be put upon the electrocardiogram. A man, 45 years of age, was suddenly seized while eating his mid-day meal with excruciating pain in the chest radiating to the left shoulder. He died at the end of 24 hours and the autopsy revealed rupture of the aorta with the formation of a dissecting aneurysm. The electrocardiographic report reads as follows: P-waves of low voltage. QRS slightly slurred. Q-waves prominent in Lead III. T-waves inverted in Lead I, diphasic and of low voltage in Lead II, upright in Lead III.

Comment. Record suggests coronary artery disease.

V. Interstitial Emphysema of the Lungs

Case VII

On February 12, 1933, I saw at Washington with Dr. W. C. Moore and Dr. J. W. Esler, a physician, 51 years of age, who had previously enjoyed excellent health. On the morning of February 8 while shaving he was suddenly seized with intense pain in the region of the heart radiating to the left shoulder. The pain lasted about half an hour and then gradually passed. When Dr. Moore examined him two hours later no definite abnormality was found. The heart and lungs were quite normal. The temperature was 98°, pulse 54 and regular, respirations 20, blood pressure, systolic 110 and diastolic 80. The following day an electrocardiogram was reported by Dr. Esler as follows: Regular rhythm: rate 60; T-waves upright in all leads; conduction interval normal; maximum QRS potential 9 mm. The blood count was normal, the leukocytes 8,550 per cubic mm. On the morning of February 11 the patient reported to Dr. Moore that during the night when lying on the left side he had heard a curious loud bubbling, crackling sound synchronous with the heart beat. His wife sitting on the bed beside him could easily hear the sound. At this time Dr. Moore could make out no abnormality whatsoever on physical examination. The heart and lungs were quite normal. The temperature was 98°, pulse 66, respirations 20, blood pressure, systolic 100, diastolic 75.

Later in the day Dr. Esler thought he heard a pericardial friction. This seemed to establish the diagnosis of coronary occlusion which had previously been suggested. When I saw the patient on the afternoon of the following day he was sitting up in bed laughing and talking, protesting that he felt perfectly well. He certainly was in good spirits and had every appearance of robust health. The temperature, pulse, respirations and blood pressure were all normal as they had been before. I examined the heart and the lungs with the greatest care and could detect nothing that was to the least degree abnormal. When I expressed surprise the patient laughingly said that he could easily produce the sound. He turned on his left side, shifted about a few moments and suddenly said, "There it is." I put my stethoscope over the apex beat of the heart and with each impulse heard the most amazing sound. It is difficult to describe. Crunching is the best adjective I can think of though it is far from apt especially since crunching has been widely used to describe pleural friction to which it bore no resemblance. It certainly conveyed the impression of air being churned or squeezed about in the tissues. It recalled an instance of pneumopericardium I had listened to years before. When the patient turned on his back the sound at once disappeared. The possibility of pneumothorax came to my mind. However, a second thorough examination of the lungs was quite negative. Still I persisted and suggested that it might be a small localized pneumothorax near the apex of the heart. The following day a roentgenogram was taken with a portable machine by Dr. E. M.

McPeak. Dr. McPeak's report reads as follows: "Examination of the chest shows the bony thorax, heart and great vessels normal in appearance. There is slight thickening of the interlobar pleura on the right side with some slight increase in density throughout the right base. The appearance in the right base is probably due to bronchiectasis. There is no other evidence of abnormality except perhaps a very slight widening of the aortic arch and the thoracic aorta."

The extraordinary sound disappeared after a few days. At the end of two weeks the patient was up and about and during the past year has led an active life and has had no symptoms of ill health. Dr. Moore examined him on February 20, 1934, and found him in excellent condition.

The course of events in this patient convinced me that he did not have coronary occlusion and yet I could not clearly understand what had caused the sudden pain and how the extraordinary sound heard over the heart had been produced. I revolved the matter in my mind again and again until four months later when I saw in the wards of The Johns Hopkins Hospital a boy with subcutaneous emphysema in the neck and emphysema of the mediastinal tissues. The moment I put my stethoscope over his heart it flashed upon me that here was the explanation for the puzzling sound I had heard over the heart of the Washington physician. I add a brief account of the illness of this patient.

Case VIII

A white boy, 17 years of age, a tin worker, was admitted to The Johns Hopkins Hospital June 25, 1933, complaining of pain on breathing. Though a delicate lad, he had previously always been well. On the day before admission at 6 p.m., while sitting quietly on a chair, he suddenly had a feeling of pressure under the sternum as though there were a lump there. Soon swelling actually appeared above the clavicles and he had severe pain on breathing deeply, on swallowing and on turning the head. He was seen in the accident room a few hours after the symptoms came on. Examination of the throat and larynx revealed no abnormality. There was subcutaneous emphysema of the tissues in the neck and over the upper part of the chest. During the night he was very uncomfortable with pain under the sternum especially on deep breathing and swallowing. He spent most of the night sitting up. The next morning he entered the hospital.

Examination: Temperature 101.2° F.; pulse 86; respirations 24; blood pressure 110 systolic and 70 diastolic.

A thin, pale, undernourished boy lying quietly in bed complaining of pain under the sternum and about the neck. He was mildly apprehensive. There was subcutaneous crepitation over the front of the neck which extended backward to the trapezius muscle on both sides and downward over the clavicles to about the second rib on the left and the nipple on the right.

The eyes were normally prominent, the pupils equal and reacted actively to light. Extraocular movements were normal. Slight enlargement of the superficial lymph nodes in neck, axillae and groins was present. The thyroid was not enlarged. The chest was long and thin with a narrow costal angle. The sternum was prominent, producing a slight degree of pigeon breast. The lungs were clear. The apex beat of the heart was in the fifth interspace 6 cm. to the left of the mid-line. The sounds were distant, barely audible. They were obscured by a loud systolic crunching sound heard all over the heart and in the left interscapular area behind. The abdomen was normal in appearance. Walls soft and relaxed. No tenderness. No mass. Liver and spleen not enlarged. Right kidney easily felt. Reflexes normally active.

Course after Admission to the Hospital: The temperature which was 101.2° on admission gradually fell and after the third day was normal. The symptoms all soon subsided and the subcutaneous emphysema and curious sound over the heart disappeared. He left the hospital well 20 days after admission. On July 31, 1933, he reported at the Out-Patient Clinic. He was feeling perfectly well and the physical examination was quite negative.

Laboratory Examinations: Blood hemoglobin 105 per cent; red blood cells 5,240,000; leukocytes 13,000.

Wassermann reaction (blood), negative.
Roentgenogram: 6/26/33. Chest: subcutaneous emphysema. Free air in the tissues of the neck and trachea; free air in the mediastinum.
7/5/33. Lungs clear.
Urine: Specific gravity 1.018; no albumin; no sugar; a few leukocytes in the sediment.

It might be objected in this instance that the peculiar sounds heard over the heart may have been due to the pressure of the stethoscope upon air in the subcutaneous tissue of the chest wall since crepitus was felt below the left clavicle. However, I am convinced that the sounds could not have been produced in this way because they occurred only with each contraction of the heart. In the following case this possibility was entirely excluded as there was no subcutaneous emphysema of the chest wall.

Case IX

A white maid, 24 years of age, came to the Out-Patient Department of The Johns Hopkins Hospital, May 31, 1930, complaining of pain in the abdomen and chest. She was examined first in the Gynecological Clinic where no important abnormality of the pelvic organs was discovered. She spoke of having spat blood now and again over a period of years. Examination in the Medical Clinic was quite negative. There was no abnormality about the heart or lungs and a roentgenogram of the chest showed the lungs to be clear. She was then referred to the Laryngological Clinic where infection of the left antrum was found. From then on she was treated in this clinic at intervals for years. The antrum was irrigated on a number of occasions. On June 18, 1931, the left ethmoidal cells were opened and drained. Five days later a radical operation was performed upon the left antrum. She recovered satisfactorily from the operations but continued to have headaches, unpleasant symptoms of nasal occlusion and a profuse purulent discharge. On the morning of July 17, 1933, the left antrum was irrigated. In the afternoon the left side of the face began to swell and the pain became more and more severe. In the evening the following note was made by Dr. James Bordley, Jr.: "Following irrigation of the left maxillary sinus the patient developed emphysema of the cheek. Late this evening she began to complain of pain about the heart accentuated by respiration. At present she is quite uncomfortable. Every now and then she sits forward with the hand pressed over the heart complaining of severe pain. When asked to localize the pain she places the finger just to the left of the sternum at the level of the sixth and seventh costal cartilages. There is no respiratory difficulty, no cyanosis, and no pain in the left shoulder or arm. Subcutaneous emphysema of left side of face is present and subcutaneous crackles extend down to the clavicles on both sides of neck. No emphysema is noted over the chest or in axillae. On auscultation over the heart there are numerous popping and crackling sounds which vary with the cardiac cycle and with respiration. The heart sounds are somewhat distant especially at the base of the heart. There is a resonant note over the manubrium. The lungs are clear. There is no evidence of pneumothorax. Impression: Emphysema of face, neck and mediastinum."

After four days the emphysema had completely disappeared and the patient was as well as before. There was slight fever during the attack, 98.6° to 100°. Leukocytes were 10,462.

Listening to a description of these episodes it may appear far fetched to say that they resemble the manifestations of coronary occlusion. However, under certain circumstances the resemblance may be very close. Not, it is true, when there is subcutaneous emphysema, but if the air escapes into the interstitial fibrous bands of the lung and travels only to the mediastinum then the similarity may be very confusing. With the escape of air and the tearing apart of the fibrous tissue there is sudden severe pain. This may be followed by fever and a slight leukocytosis. The systolic crunching sound which is heard over the heart may easily be mistaken for a pericardial friction. If the observer is not familiar with the peculiar symptoms which accompany this accident, coronary occlusion may be erroneously diagnosed.

HEPATIC FUNCTION IN RELATION TO HEPATIC PATHOLOGY: EXPERIMENTAL OBSERVATIONS *

By Frank C. Mann, M.D., *Rochester, Minnesota*

It is the ideal and ambition of the investigator in experimental medicine to discover new facts by the experimental method in order to aid the clinician in his work of preventing disease and healing the sick. While I would object strenuously to the viewpoint that all experimental research should be practical in nature or have a practical aspect, because it is not possible to evaluate research in terms of practical application, nevertheless the experimental investigator with a clinical point of view strives to undertake to investigate those problems in which the answer may ultimately benefit the patient. This was the object which my associates and I had in mind when we undertook a series of investigations on the functions and experimental pathology of the liver. The results of our investigations have only partially fulfilled our hopes and must be considered at present as having accomplished little more than preparation for what we hope will be more fruitful investigations. A general review only will be presented since the scope of our subject is broad and the number of investigations we have made on it numerous.

The liver has many definite and important known functions. Knowledge of the physiologic activity of the liver, even though this activity is vital and manifold, has not been of great value to clinical medicine owing mainly to a lack of knowledge of how the hepatic functions are affected by pathologic changes in the organ. From the experimental standpoint, therefore, the next step, after determining some of the functions of the liver, was to investigate the effect of hepatic injury on these functions. This necessitated the experimental production of pathologic lesions of the liver and their study.

Many methods have been used to produce pathologic changes in the liver and to decrease hepatic function. These include (1) employment of the more or less specific hepatic poisons, as chloroform, phosphorus, carbon tetrachloride, and so forth; (2) partial removal of the organ; (3) obstruction of the biliary outflow; (4) shunting of the portal blood away from the organ, and other less used methods.

One fundamental characteristic of the liver usually has been responsible for defeating the purpose of most of the experiments performed in order to reduce the functional capacity of the liver. Restoration to some extent occurs in most organs of the body after partial removal or injury. It occurs to a very remarkable extent in the liver. This characteristic of the liver makes it difficult to produce experimentally a decrease in the functioning

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934. From the Division of Experimental Medicine, The Mayo Clinic.

hepatic tissue to such an extent that the hope would be justified that the physiologic activity had been reduced to an amount that could be measured.

The effect of hepatic poisons on the liver is usually transitory, and if the animal recovers from the acute effects of the drug, the hepatic parenchyma is restored to almost its normal condition. It is only by repeated administration of such substances that a more permanent pathologic change can be made in the liver. Although there are many substances which will produce a more or less specific hepatic injury, for purposes of experimental investigation carbon tetrachloride is the best so far discovered. As was shown by Lamson [18] and his associates, repeated administration of this substance in appropriate doses for several weeks produces a condition of the liver similar to cirrhosis as seen in man.

Partial removal of the liver, from individuals of those species of animals in which removal is anatomically possible, produces a decrease in hepatic tissue but not for a very long time. Restoration of the normal organ, even after as much as 70 per cent has been removed, is usually rapid and complete.[14, 17]

Obstruction of the biliary outflow injures one function of the liver, that of secreting bile, but does not greatly interfere with the other hepatic functions or greatly injure the hepatic parenchyma unless the obstruction is maintained for several months. By that time the effect of the obstruction itself on the other tissues of the body is so great that it is hazardous to interpret the results of functional studies in terms of hepatic injury.

The shunting of the portal blood from the liver by an Eck fistula produces within a few weeks a decrease in the size of the liver by about one-half. This atrophy, however, usually is not of sufficient magnitude to be of value for studies of hepatic insufficiency. Our studies on animals with an Eck fistula have been disappointing.

We have found that a combination of these various methods furnishes a preparation in which functional hepatic tissue is permanently decreased. We discovered that restoration of the liver after partial removal either did not occur, or only to a limited extent, if (1) the portal blood was shunted away from the organ, (2) if biliary obstruction was present, or (3) if cirrhosis existed. If any one of these procedures was carried out, that is, making an Eck fistula, obstructing the common bile duct, or producing cirrhosis, and if a portion of the liver subsequently was removed, a definite and permanent decrease in hepatic tissue was secured.[22] It was sometimes possible to decrease the hepatic tissue to 15 per cent or less of the normal amount. The results of the investigation which we wish to report were secured from observations made in part on animals from which the liver had been totally removed, partially removed, injured transitorily with chloroform or phosphorus, or made cirrhotic with carbon tetrachloride. Other observations were made on animals from which the liver had been partially removed after an Eck fistula had been made, after obstruction of the biliary outflow, or after the development of cirrhosis.

In attempting to evaluate methods for estimating hepatic function, several facts concerning the functional characteristics of the liver should be constantly kept in mind: (1) The capacity of the normal liver to carry on its many functions is greatly in excess of the normal needs of the organism. Although this statement is probably true of all organs of the body, it is particularly applicable to the liver. It would thus seem to be extremely difficult ever to measure the capacity of the normal liver in regard to any one of its functions without producing a very abnormal physiologic condition. (2) The capacity of the liver to perform its functions is dependent on many factors, and may change with extreme rapidity. Determination of a specific hepatic function of a particular animal at a definite time, even if it could be made with reasonable accuracy, would not necessarily be the same after a very short period of time. (3) A decrease in one of the functions of the liver does not necessarily mean that all functions, or any other one of its many functions, are equally impaired or even at all injured. There seems to be a dissociation of functions of the liver, so that it is possible for one to be defective in an otherwise normally functioning organ. (4) Most of the functions of the liver are so intimately associated and correlated with the physiologic activity of other organs or tissues that it is difficult or impossible definitely to delineate the hepatic factor. Hepatic activity is often only a part, although important and often vital, of a physiologic process in which one other organ or tissue, or more than one, is involved. (5) Finally it should be noted that the liver maintains all its known and therefore its possible measurable functions with extreme stubbornness. Normal hepatic functions are carried on by a very small amount of functioning tissue. An animal without a liver may be totally unable to maintain a certain physiologic process, while an animal with only a small percentage of its normal amount of hepatic tissue seemingly may function as well in this respect as when all its liver was present.

Studies of the Bile and Its Constituents

The function of the liver which in the past has been of most interest to the clinician is secretion of bile. This is owing to the fact that the bile contains a pigment which, when retained in the body, excreted in the urine, or prevented from reaching the digestive tract, furnishes definite evidence to the clinician that something may be wrong with the function of the liver or the discharge of its external secretion. Study of this secretion is handicapped by the fact that it is poured into the intestine and is not readily accessible for observation. It has been necessary, in order to overcome this difficulty, to study the more important constituents of bile as they may be retained in the body or appear in the urine.

The bile contains several substances, three of which appear to be the most important: cholesterol, bilirubin, and bile acids. Too little is known at present in regard to cholesterol, either its origin or significance in the bile,

to justify a consideration of it as a possible indication of hepatic function, even if it were possible to obtain the bile directly and to estimate the cholesterol quantitatively. Bilirubin and the bile salts have been important substances in the search for a method of estimating hepatic function.

Because jaundice was the first clinical sign observed of hepatic dysfunction, bilirubin has been in the past, and still is probably, the most important substance used to indicate hepatic injury. Physiologically several important facts are known concerning bilirubin which have important bearings on its employment as an indicator of hepatic function. These facts are (1) bilirubin is formed from hemoglobin [26]; (2) a considerable portion of the bilirubin found in the bile is formed outside the liver [21, 23, 24, 25]; (3) only a small portion of the normal liver is necessary to excrete all the bilirubin formed in the body [29]; (4) only bilirubin which has reached the hepatic cells gives the so-called direct van den Bergh reaction.[7] Although satisfactory methods have been developed for estimating the amount of bilirubin retained in the blood, such as the van den Bergh method [1] and the icteric index,[30] and though the data so secured may be of great clinical value, the facts mentioned definitely indicate that such data do not suffice for quantitating hepatic injury, as the amount of bilirubin formed and the rate at which it forms depend on several factors, many of which determine or change the rate of formation of bilirubin and the amount of this substance formed. Probably the most important of these, which is not hepatic, is the amount of hemoglobin available for making bilirubin, and the amount of hemoglobin in turn depends on several factors, as destruction of blood, loss of blood, and diet.

Bollman and I [9] have made attempts to determine whether we could correlate the amount of bilirubinemia with the amount of hepatic tissue present, or with the extent of hepatic injury. We found that the amount of bilirubin in the blood, as previously has been suggested, depends on many other factors than hepatic injury. For instance, an animal with obstruction to the biliary outflow will have a large amount of bilirubin in the blood a few days after the beginning of the obstruction, and at a time when the liver appears almost normal, and will have only a small amount of bilirubin in the blood several months after the obstruction, when the liver is very severely injured. An almost undetectable amount of bilirubin may be present in the blood of a dog the hepatic tissue of which consists of a single cirrhotic lobe, while intense jaundice will occur in a normal animal after administration of toluylendiamine, at a time when very little hepatic injury is demonstrable.

The bile salts appear to be products of activity of hepatic cells and to have at least one known function, that of assisting in the digestion of fat. Although no completely satisfactory methods are available for the determination of bile salts in body fluids, such methods as exist are sufficient to afford considerable information about the metabolism of these substances. Accurate methods for determination of bile salts in the bile have permitted Whipple [36] and his collaborators to draw the following conclusions from

their studies of animals with complete biliary fistulas: Daily excretion of bile salts is constant under constant dietary and physical conditions; dietary factors may affect the amount of bile salts formed; bile salts administered by vein or by mouth are rapidly and quantitatively excreted in the bile; the liver is probably responsible for the elaboration of bile salts, and slight hepatic injuries may greatly reduce the amount of bile salt formed and excreted. Bollman has modified the method of Gregory and Pascoe [16] so that he has obtained fairly satisfactory results with the determination of bile salts in the urine and blood of dogs. He has made the following observation on the formation and determination of bile salts in normal animals, and on animals with different types and degrees of hepatic injury.[3]

The normal animal excretes only traces of bile salts in the urine, and bile salts are not definitely detectable in normal blood. Following intravenous administration of glycocholates or taurocholates only a small portion appears in the urine and the injected material rapidly disappears from the blood. Large amounts may be given by mouth without appearing in the blood, urine or feces. After complete removal of the liver, bile salts do not appear to be formed, but administered bile salts are quantitatively excreted in the urine within a few hours after injection. If biliary excretion is prevented by ligation of the biliary ducts, bile salts are excreted in the urine, but not all of the injected bile salts are recovered in the urine. It would appear that the liver plays a predominant part in destruction of bile salts as well as in their formation.

In the experiments with animals in which bile fistulas have been made, and with animals with complete obstructive jaundice, both formation and destruction of bile salts appear to be influenced by the condition of the liver. Excretion of bile salts in the urine in the presence of obstructive jaundice is definitely less than that in the bile in the presence of biliary fistulas. This appears to be due to the destruction of bile salts in the presence of obstructive jaundice, since administered bile salts are not all excreted, as they are in the presence of biliary fistula. Various agents which affect the liver reduce excretion of bile salts. Infection of the intrahepatic ducts, toluylendiamine, chloroform, carbon tetrachloride, or phosphorus poisoning may reduce excretion of bile salts to less than one-tenth of its former value. The greatest reduction occurs at the time of greatest hepatic injury, but marked reduction in excretion of bile salts may be obtained with hepatic injury too slight to be detected by ordinary histologic examination. The ability of the liver to destroy bile salts may not be altered, so that it would appear that the ability of the liver to form bile salts is easily impaired. Hepatic injury by toluylendiamine, carbon tetrachloride, or chloroform sufficient to give rise to urinary excretion of bile pigment, usually is accompanied by excretion of increased amounts of bile salts in the urine. If animals retain bile pigment in the blood from injury to the liver, or from uncomplicated biliary obstruction, increased amounts of bile salts may be found in their blood. Severe

hepatic injury reduces the amount of bile salts found in the blood, apparently by reducing the formation of these substances.

A fairly accurate index of the condition of the livers of dogs with complete biliary obstruction was obtained by following the concentration of bile salts in the urine. The greater the excretion of bile salts under these conditions, the better has been the condition of the liver. Jaundice develops after a slight or moderate amount of hepatic injury; obstruction is associated with moderate excretion of bile salts. Improvement of the condition of the liver decreases the excretion of bile salts, but additional injury to the liver also diminishes excretion of bile salts. While the results of these observations would indicate that the concentrations of bile salts in the blood and urine are significant in postulating hepatic injury, it is questionable if such data can be used to quantitate hepatic function. The fact that the liver appears both to make and to destroy these substances would seem to preclude such a possibility.

The Use of Dyes

The fact that the liver excretes many other substances, such as minerals and dyes, in the bile, has led to the common use of the rate of excretion of certain dyes as a method of estimating hepatic function. Since it is not the normal function of the liver to excrete these foreign substances, and since some of these tests are of clinical value, we believe they should not be called tests of hepatic function.

Most of our studies of dye methods for estimating hepatic function have been made by observing the rate of disappearance from the blood of an injected dye, such as bromsulphthalein or rose bengal. Many dyes may be used which appear to be specifically excreted by the liver. With a dose of dye that is entirely eliminated from the blood of normal animals in a few minutes, large amounts of the dye are found to be present in the blood several hours after injection into animals with complete biliary obstruction, or into animals from which the liver has been completely removed. Partial removal of the normal liver from animals, however, does not alter the excretion of dye in direct proportion to the amount of liver removed. If the remaining portion of liver is not injured by anesthesia or surgical trauma, little influence is noted after removal of more than half of the hepatic tissue, and a small amount of hepatic tissue (10 per cent) may take only twice as long to clear the blood of dye as is required by the liver of the normal animal. It should be emphasized that the remaining portion of liver of these animals is essentially normal, and that in all probability the normal hepatic cells do not become blocked by the dye but continue to pass it into the bile. In this way the fewer cells appear to be almost as efficient as a larger number working with a relatively smaller concentration of dye.

We have also attempted to correlate the results of dye tests with the amount of gross and microscopic pathologic change in the livers of animals

in various stages of cirrhosis caused by carbon tetrachloride. Specimens were immediately obtained at biopsy following completion of the dye test. It was immediately obvious that it was impossible to interpret the microscopic pathologic change in the liver from its gross appearance at exploratory laparotomy, particularly in the group of cases in which the liver appeared normal to gross examination, but had extensive microscopic changes. In general, the extent of pathologic change in the hepatic cells appeared to parallel the retention of the dye. The scirrhous changes in the liver apparently bore no relation to the excretion of dye. There were many exceptions, in which the results of dye tests failed to correspond to the pathologic change found in the liver. Some normal animals gave definite evidence of retention, and some animals with extensive gross and microscopic hepatic injury failed to retain any dye.

It would appear justifiable to conclude from these observations, in so far as the experimental animal is concerned, that the rate at which the liver removes a dye from the blood stream indicates how fast the liver will remove that particular dye from the blood stream at that time. When taken by itself it is not reliable in quantitating the extent of pathologic changes in the liver or how well the many other functions of the organ are being performed at the time the test was made. On the other hand, it may indicate hepatic injury and is probably as good a method as any developed to date for doing this.

Estimates Based on Carbohydrate Metabolism

One of the most important functions of the liver has to do with carbohydrate metabolism. The liver is apparently either directly or indirectly responsible for maintaining the concentration of glucose in the blood. In this capacity it stores carbohydrate in the form of glycogen, which can readily be converted into glucose, and it can also make carbohydrate from proteins, and glucose from some of the other sugars. So many attempts have been made to measure hepatic function, and so many methods have been developed for it, based on this phase of hepatic activity, that it is impossible to review them adequately here.

Most of the tests concerning carbohydrate metabolism have been based on utilization of one of these sugars: dextrose, levulose, or galactose. All three are used in tolerance tests, and in addition, changes in the dextrose content of the blood following administration of drugs which produce hyperglycemia have been taken as criteria of hepatic function. Although it is true that hepatic activity is an important factor in removing an excess of dextrose from the animal organism and that there is a marked difference between the dextrose tolerance of a normal animal and that of a dehepatized animal,[32] the fate of dextrose in the animal organism depends on so many extrahepatic factors that only under very special conditions could a change in glucose tolerance indicate impaired hepatic function. The use of a hyperglycemic agent to indicate hepatic injury is based on the facts that the liver

is the essential organ for producing hyperglycemia,[19, 27] and usually an injured liver does not contain as much glycogen as the normal organ; therefore the hyperglycemia should be less in the presence of an injured liver. It should be noted that the glycogen content of the normal liver may vary within wide limits, from a minimum of less than 1 per cent to a maximum, as Butsch [13] has shown, of more than 20 per cent. It can thus be seen that only under special conditions could this test be of significance. Bollman and I,[9] using epinephrine as the agent for producing hyperglycemia, have attempted to use this test on our animals with reduced hepatic parenchyma, but have found it unreliable. However, it might be employed to advantage for specific purposes.

Although the liver does make glycogen from levulose, the muscles can do this also, and levulose can be utilized by an animal without a liver.[6] Consequently, it is difficult to understand how a levulose tolerance test could be used to measure hepatic injury.

Theoretically it should be possible to indicate hepatic injury by a galactose tolerance test, as the utilization of this sugar appears to depend mainly on the liver.[32] However, as Millet [31] has shown, the difficulty in employing this test experimentally is due to the wide difference in rate of utilization of galactose by the normal animal.

When all the known factors that enter into the metabolism of carbohydrate are considered: the rapidity with which it may be utilized by the normal animal and the slowness of its utilization by the fasted animal; its storage in large amounts in two major sites, liver and muscle, and the difference in the manner of utilization of the glycogen in these two sites; the enormous influence of insulin on it; the formation of fat from it; and when it is further recognized that there are probably many more factors to be discovered, as the recent work on the pituitary body and suprarenal gland would indicate, it would seem that the utilization of any phase of carbohydrate metabolism to measure hepatic activity, even though the liver has a major part in such metabolism, is almost hopeless. All the investigations on this problem made in our laboratory would tend to confirm this pessimistic outlook.

Determinations Based on Protein Metabolism

The liver is essential for normal protein metabolism. Deaminization,[12] formation of urea,[5, 10] and oxidation of uric acid to allantoin [8, 11] depend on the liver. None of these processes, when measured in the usual manner, occur in the dehepatized animal. On the other hand, an animal with greatly reduced hepatic parenchyma may carry on these processes at almost the same rate as the normal animal, with the exception of the formation of allantoin from uric acid.[20] The latter process is decreased by hepatic injury.[4]

Green [15] has studied the nitrogen partition in the blood and urine of dogs, when they were normal and after the development of various degrees of cirrhosis produced by carbon tetrachloride. He administered small quan-

tities of carbon tetrachloride to dogs, two or three times a week, for periods of from two to seven months. The animals were maintained under standard conditions and the total urinary excretion was analyzed daily for the main nitrogenous constituents. At various periods of time the nitrogenous constituents of the blood were also determined. From time to time the animals were etherized and the liver explored, its condition noted, and a specimen secured for histologic examination.

Definite lesions were produced in all of the animals. The lesions were progressive in nature, as was determined by exploration and histologic examination of the specimen secured. In the animals to which the drug was administered for several months, the liver became markedly cirrhotic.

During the production of the hepatic lesions, there were changes in both actual and relative amounts of nitrogenous constituents excreted in the urine. There was a decrease in the amount of urea, and an increase in the amount of ammonia, amino acids, and uric acid. Creatinine accounted for a fairly constant percentage of the total amount of nitrogen excreted. The most marked early changes were seen in the amount of amino acid excreted, which would almost double within a few days after beginning administration of the drug. Later, the amount of uric acid was the most altered, the increase amounting to several hundred per cent.

Our observations on the effect of hepatic injury on those phases of nitrogen metabolism in which the liver has been definitely proved to be involved, indicated that the hepatic injury cannot be quantitated by changes in excretion of the essential nitrogenous constituents. There remains, however, the possibility that a method of measuring hepatic function may be developed from utilizing one of its activities in relation to metabolism of nitrogen.

Estimates Depending on So-Called Hepatic Detoxication

The liver usually has been considered as the site of destruction of many toxic substances. There is no question but that hepatic tissues will render inert many substances which are harmful to the organism. However, in only a limited number of instances has it been proved that the liver actually destroys the active agents. It is known that the liver is the site of destruction of almost all strychnine [34] that gains access to the body, and that it will destroy more nicotine [2] than all the other tissues of the body. On the other hand, it is not more active in causing epinephrine [28] and ephedrine [35] to disappear than the other tissues of the body. At present there is no method of determining whether the liver will destroy any given substance without direct experimentation. Adequate physiologic methods are at hand to determine whether the liver specifically destroys a substance, provided the substances under investigation can be estimated either biologically or chemically in the blood or tissues.

Many tests of hepatic function have been devised, based on the ability of the liver to destroy certain substances. In order to justify employment

of any substance for this purpose, it should first be demonstrated that the liver actually destroys all or a major portion of the substance, and it is necessary to have a method of quantitating the substance either directly or indirectly. Too often the sponsor of a given test has not troubled himself to fulfill both of these necessary requirements. There are very few tests, based on this phase of hepatic activity, in which it has been consistently proved that the test substance is actually destroyed in the liver.

Some very serious objections are encountered in attempting to measure the ability of the liver to destroy a given substance. Many of the substances so used are toxic to the liver or to the organism as a whole. This undesirable effect will be greatest in those instances in which the test is most desired; namely, where the hepatic parenchyma is reduced. The effect of the substance on the liver or organism often depends on the physiologic state of the liver at the time the substance was administered. The differences in effect of certain hepatic poisons on the glycogen-filled and glycogen-depleted liver is a good illustration. Furthermore, there may be a marked difference in the response to a given substance, depending on whether it is given when the subject is in a fasting or in a digesting state.

Owing to the considerations named we have not felt justified in using many of these tests in our investigations. Early in our work we discovered that although many of the substances used in an attempt to measure the capacity of the liver to destroy them would, in a given amount, be harmless to the normal dog, they might, in the same dose, cause severe reaction or death of animals with greatly reduced hepatic parenchyma. It should be noted, however, that there is a definite and possibly valuable field for investigators to discover a nontoxic substance, destroyed by the liver, which can be measured by some suitable method. At present such a substance does not appear to be available.

Numerous other supposed methods for measuring hepatic function have been described. Some of these tests are based on physiologic processes which have never been proved to be due to hepatic activity. Few of the tests, other than those previously given, appeared to have sufficient merit to justify investigations on experimental animals in our laboratory.

It should be noted that in our investigations we have taken the gross and histologic appearance of the liver as the standard for indicating the amount of hepatic injury. While we do not believe that such a standard is adequate, until a better one is developed it must suffice. For this reason I have confined this paper to a relation of our observations on attempts to correlate changes in known functions or activities of the liver in relation to the amount of hepatic tissue present or to the pathologic condition of the organ at the time the observations on function were made.

Summary

A series of studies has been made to determine if a quantitative relationship could be found between the amount of apparently functioning

hepatic tissue and the capacity of such tissue to maintain any one of the many known functions of the liver. Methods were employed which would produce definite and permanent decrease in hepatic parenchyma. The amount of hepatic tissue possessed by the animals studied varied from normal to none and included a series of animals in which the hepatic injury was graduated from that in which the liver was severely injured acutely to that in which only a small amount of markedly cirrhotic hepatic tissue remained. Observations usually were made of the gross and microscopic appearance of the liver immediately after completion of each study of function.

Several important physiologic processes cease immediately after the liver is totally removed. Other processes are greatly modified. On the other hand, extreme reduction in hepatic parenchyma, as much reduction as it was possible to produce and have the animal survive, produced slight or no changes in those physiologic processes which were abolished or modified by total removal of the organ. The results of our studies would indicate that extreme caution must be used in attempting to postulate the pathologic condition of the liver of an individual by the results of the so-called hepatic function tests. In these studies none of the many methods for measuring hepatic functional capacity which we tried were wholly reliable in indicating to us the approximate extent of reduction of hepatic parenchyma, and injury to hepatic parenchyma, as determined by gross and microscopic observations made immediately after completion of the test. While several of the tests may be of value clinically, it would seem that unless their use is combined with other methods of determining hepatic disease, they may cause serious error.

BIBLIOGRAPHY

1. VAN DEN BERGH, A. A. H.: La recherche de la bilirubine dans le plasma sanguin par la méthode de la réaction diazoique, Presse méd., 1921, i, 441–443.
2. BIEBL, M., ESSEX, H. E., and MANN, F. C.: Studies on physiology of liver; rôle of the liver in destruction or inactivation of nicotine, Am. Jr. Physiol., 1932, c, 167–172.
3. BOLLMAN, J. L.: Unpublished data.
4. BOLLMAN, J. L., and MANN, F. C.: Changes in excretion of uric acid produced by experimental hepatic insufficiency, Proc. Soc. Exper. Biol. and Med., 1926, xxiii, 685–687.
5. BOLLMAN, J. L., and MANN, F. C.: Studies on physiology of the liver; effect of removal of liver on formation of ammonia, Am. Jr. Physiol., 1930, xcii, 92–106.
6. BOLLMAN, J. L., and MANN, F. C.: Physiology of liver; utilization of fructose following complete removal of liver, Am. Jr. Physiol., 1931, xcvi, 683–695.
7. BOLLMAN, J. L., and MANN, F. C.: Studies of physiology of liver; van den Bergh reaction in jaundice following complete removal of liver, Arch. Surg., 1932, xxiv, 675–680.
8. BOLLMAN, J. L., and MANN, F. C.: Studies on physiology of liver; allantoin and uric acid following total removal of liver, Am. Jr. Physiol., 1933, civ, 242–246.
9. BOLLMAN, J. L., and MANN, F. C.: Unpublished data.
10. BOLLMAN, J. L., MANN, F. C., and MAGATH, T. B.: Studies on physiology of liver; effect of total removal of liver on formation of urea, Am. Jr. Physiol., 1924, lxix, 371–392.

11. Bollman, J. L., Mann, F. C., and Magath, T. B.: Physiology of liver; uric acid following total removal of the liver, Am. Jr. Physiol., 1925, lxxii, 629–646.
12. Bollman, J. L., Mann, F. C., and Magath, T. B.: Studies on physiology of liver; effect of total removal of liver on deaminization, Am. Jr. Physiol., 1926, lxxviii, 258–269.
13. Butsch, W. L.: Glucose tolerance and the glycogen storage capacity of the dog, Am. Jr. Physiol., 1934, cviii, 639–642.
14. Fishback, F. C.: Morphologic study of regeneration of liver after partial removal, Arch. Path., 1929, vii, 955–977.
15. Green, G. F.: Unpublished data.
16. Gregory, R., and Pascoe, T. A.: Quantitative determination of bile acids by means of new color reaction and monochromatic light, Jr. Biol. Chem., 1929, lxxxiii, 35–42.
17. Higgins, G. M., and Anderson, R. M.: Experimental pathology of liver; restoration of liver of white rat following partial surgical removal, Arch. Path., 1931, xii, 186–202.
18. Lamson, P. D., and Wing, R.: Early cirrhosis of liver produced in dogs by carbon tetrachloride, Jr. Pharmacol. and Exper. Therap., 1926, xxix, 191–202.
19. Mann, F. C.: The relation of the liver to metabolism, Harvey Lectures, 1927–1928, xxiii, 49–75.
20. Mann, F. C., and Bollman, J. L.: Liver function tests, Arch. Path. and Lab. Med., 1926, i, 681–710.
21. Mann, F. C., Magath, T. B., and Bollman, J. L.: Studies on the physiology of the liver; formation of bile pigment after total removal of the liver, Am. Jr. Physiol., 1924, lxix, 393–409.
22. Mann, F. C., Fishback, F. C., Gay, J. G., and Green, G. F.: Experimental pathology of liver, Arch. Path., 1931, xii, 787–793.
23. Mann, F. C., Sheard, C. H., and Bollman, J. L.: Physiology of liver; extrahepatic formation of bilirubin, Am. Jr. Physiol., 1925, lxxiv, 49–60.
24. Mann, F. C., Sheard, C., and Bollman, J. L.: Evaluation of relative amounts of bilirubin formed in liver, spleen and bone marrow, Am. Jr. Physiol., 1926, lxxviii, 384–392.
25. Mann, F. C., and others: Formation of bile pigment from hemoglobin, Am. Jr. Physiol., 1926, lxxvi, 306–315.
26. Mann, F. C., and others: Studies on physiology of the liver; liver as site of bilirubin formation, Am. Jr. Physiol., 1926, lxxvii, 219–224.
27. Markowitz, J.: Glyconeogenesis, Am. Jr. Physiol., 1925, lxxiv, 22–35.
28. Markowitz, J., and Mann, F. C.: Rôle of liver and other abdominal viscera in destruction of epinephrine in body, Am. Jr. Physiol., 1929, lxxxix, 176–181.
29. McMaster, P. D., and Rous, P.: Biliary obstruction required to produce jaundice, Jr. Exper. Med., 1921, xxxiii, 731–750.
30. Meulengracht, E.: Ein Bilirubinkolorimeter behufs klinischer Bestimmung der Bilirubinmenge im Blute, Deutsch. Arch. f. klin. Med., 1921, cxxxvii, 38–46.
31. Millet, R. F.: Unpublished data.
32. Pollack, H., Millet, R. F., Bollman, J. L., and Wilder, R. M., Jr.: Glucose tolerance of dehepatized animals, Proc. Staff Meet. Mayo Clinic, 1933, viii, 557–558.
33. Power, M. H., Bollman, J. L., and Mann, F. C.: Unpublished data.
34. Priestley, J. T., Markowitz, J., and Mann, F. C.: Studies on physiology of the liver; detoxicating function of liver with special reference to strychnine, Am. Jr. Physiol., 1931, xcvi, 696–708.
35. Thorp, E. G., Essex, H. E., and Mann, F. C.: Studies on fate of ephedrine in dog, Am. Jr. Physiol., 1933, cv, 389–392.
36. Whipple, G. H., and Smith, H. P.: Bile salt metabolism; liver injury and liver stimulation, Jr. Biol. Chem., 1930, lxxxix, 727–738.

BRONCHOSCOPY IN PULMONARY DISEASE

PRESENT STATUS AS AN AID IN DIAGNOSIS AND TREATMENT*

By GABRIEL TUCKER, M.D., *Philadelphia, Pennsylvania*

THE use of the bronchoscope as an aid in the diagnosis and treatment of diseases of the lung has been practically a development of the last decade. Before that time the bronchoscope was used chiefly for the removal of foreign bodies. The modern bronchoscopic technic, using the distally lighted tube of Jackson, without general anesthesia, has widened the field of its usefulness to such an extent that bronchoscopy is indicated in practically every disease of the lung, at some time during its course, in some particular patient. In modern bronchoscopy general anesthesia is not required. In acute inflammatory conditions of the lung, as well as in dyspnea produced by obstructive lesions, general anesthesia is contraindicated, and in these conditions bronchoscopy may be of the greatest aid both in diagnosis and treatment. When we speak of modern bronchoscopy we refer to the technic as originated by Dr. Chevalier Jackson, and as developed by him and his coworkers in the various bronchoscopic clinics in Philadelphia.

Personal course postgraduate teaching has created a world-wide interest in bronchoscopy. By intensive courses for special instruction in bronchoscopic technic and the clinical application of the procedure, established in one school, the Graduate School of Medicine of the University of Pennsylvania, 636 physicians from the United States have received preliminary training in cadaver and dog work and clinical instruction in bronchoscopy. These physicians have come from practically every large city in every state in the United States. There have come also 87 student physicians from 19 foreign countries and states, including Canada, the South American States, the British Isles, three Central European states, China, Japan, Australia, South Africa and New Zealand. These student physicians were for the most part well established otolaryngologists prior to their taking the work in bronchoscopy. With adequate equipment and a trained personnel they have carried on the work on their return home and many reports have come to us of the success of their work in bronchoscopy.

The aid rendered by bronchoscopy is so essential both in diagnosis and treatment that the time will come when a bronchoscopic clinic will be as much a part of a hospital that treats pulmonary diseases as is the roentgenologic department. Bronchoscopy will, however, always supplement roentgenology in the matter of diagnosis, because the function of the bronchoscope

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934.
From the bronchoscopic clinics of the University of Pennsylvania, the Hospital of the University of Pennsylvania and the Graduate Hospital of the University of Pennsylvania.

is to look into the lung and the function of the roentgen-ray is to look through it.

Bronchoscopy as an Aid in Diagnosis. The first bronchoscopic examination is essentially a diagnostic study and in every case will give findings supplementary to other methods of examination. The larynx, trachea and larger bronchi can be inspected without general anesthesia by the use of distally lighted instruments. They are made of such size that even the new-born infant can be examined [1] without trauma, if the proper technic is followed.

Among the points noted in the bronchoscopic examination may be mentioned the appearance of the bronchial mucosa, the quantity and character of secretion, evidence of abnormality of the lumen of the trachea and bronchi, evidence of abnormal mobility, fixation or deviation of the trachea and bronchi and, finally, a careful inspection of the bronchial movements during respiration and cough. The location and extent of the lesion as seen intrabronchially is of first importance. The origin of pus or abnormal secretions from a branch bronchus gives an indication of the lesion in the area of lung supplied by the branch bronchus in question. The relative quantity of air that is passing in and out may be roughly estimated. The presence of bronchial dilatation, compression stenosis, intrabronchial lesion, growths, ulceration or infiltration can be readily determined. The significance of bronchoscopic findings should be interpreted with a knowledge of the findings obtained by the internist on physical examination and the results of roentgenologic studies. The removal of secretions uncontaminated by mouth organisms, and of specimens of tissue for biopsy, where the appearance of the local lesion in the opinion of the bronchoscopist justifies it, will give positive information that cannot be obtained by any procedure other than bronchoscopy.

Bronchoscopy for Treatment. The purpose of bronchoscopic treatment is to establish and maintain a functionally normal airway throughout the tracheobronchial tree so that there may be a state of normal ventilation and drainage in the lung. Bronchoscopic aid is principally through the removal of obstruction. Obstruction may be due,

1. To foreign body, aspirated or endogenous;
2. To stenosis or deformity of the bronchi;
3. To tissue obstruction from inflammatory or neoplastic change;
4. To secretion, normal or abnormal.

Foreign Body. Bronchoscopic removal of foreign body, with 98 per cent cure, is generally accepted as the only worthwhile method of treatment. This applies either to aspirated or to endogenous foreign bodies. Bronchoscopic removal is accomplished by the use of forceps through the bronchoscope and, by those trained in bronchoscopic procedure, is accomplished without general anesthesia. In cases where the foreign body has passed beyond the point where it can be seen through the bronchoscope,

biplane fluoroscopic guidance may be used. If the bronchoscopist and roentgenologist have mastered a coöperative technic, the procedure is usually without serious risk. In cases of foreign body where the density of the object is such that it can be localized only on the roentgen-ray film and not fluoroscopically, the technic of Pancoast and Pendergrass can be used and opaque markers placed in such a position that roentgenoscopic localization may be made and bronchoscopic removal successfully carried out under fluoroscopic guidance.[2] (See Case 2.)

Bronchial Stenosis. It is evident that the character of the lesion producing the stenosis will determine the desirability of bronchoscopic dilatation. A simple cicatricial stenosis of the bronchus may be dilated readily by direct vision by use of the bronchoscope. A compression stenosis may also be dilated bronchoscopically. The nature of the compression should, however, be known and its character should determine the method of treatment.

Stenosis due to inflammatory tissue is frequently amenable to bronchoscopic treatment. Benign endobronchial neoplasms may be removed bronchoscopically. Malignant tissue may be removed, and radon may be implanted in obstructing tissue, with removal of obstruction and relief of the secondary infective processes that so frequently are due to obstruction of the bronchus by malignant neoplastic tissue. In cases of cancer of the lung with bronchial stenosis, the results of irradiation treatment can best be determined by bronchoscopic examination.

Bronchoscopic Removal of Secretions. The bronchoscopic aspiration and removal of secretions that obstruct the airway is probably the most important contribution of the bronchoscope, aside from foreign body removal. In certain conditions where the cough mechanism has been temporarily impaired, postoperatively or post-partum, acute edema of the lungs and acute obstruction by retained secretion result, as in massive collapse of the lungs. The patient is unable to free the tracheobronchial tree from obstruction. The same conditions sometimes occur in asthma.[3] In this type of case the mechanical removal of obstructing secretion through the bronchoscope prevents asphyxial death and produces a cure that seems little short of miraculous. In inflammatory lesions, particularly in postoperative pulmonary complications, bronchoscopic removal of obstruction prevents the more serious lesions such as lung abscess, etc. In subacute and chronic pulmonary infections bronchoscopy may prevent bronchiectasis. This is particularly true of unresolved pneumonia, purulent tracheobronchitis, purulent tracheobronchitis with drowned lung, and drowned lung where the secretions are retained after the removal of foreign body. The bronchoscopic removal of secretions from the bronchi aids ventilation and drainage and allows the inflammatory processes to resolve. Repeated bronchoscopic aspiration has, in many patients, completely restored the lung to normal.

Bronchoscopic aspiration removes the secretion in two ways. First, by direct aspiration through the bronchoscope or aspirating tube. With

a flexible-tipped aspirating tube, bronchi that diverge at an angle from the main bronchi may be aspirated. The curved flexible tip permits aspiration around the corner. Second, bronchoscopic treatment brings about removal of secretion by the production of "selective cough."

"Selective Cough" as a Means of Pulmonary Drainage. On the introduction of the bronchoscope or aspirating tube into the uncocainized area of lung, there occurs a deep inspiratory effort with an extreme widening of the bronchial orifices and a violent expiratory effort which frequently can be seen to force casts of the smaller bronchi and plug-like masses of purulent secretion into the lumen of the larger bronchi in front of the bronchoscope. The removal of the obstructing material from the smaller bronchi allows free drainage of the area of lung beyond, and as a result, we find that the patient frequently continues for several days to bring up large quantities of secretion. During this time there will be evidence on physical examination that the lung is clearing. This is one of the most important results of bronchoscopic aspiration.

Bronchoscopic Medication and Disinfection in Pulmonary Disease. The introduction of medication bronchoscopically does not have a satisfactory status at the present time. It certainly is undesirable to instil oils into the lung as medication, or to flood the lung with anything in the nature of an antiseptic solution. The introduction into the larger bronchi of a mild antiseptic solution such as 1 to 10,000 mercurophen, followed by bronchoscopic aspiration, may be desirable, not so much because of the disinfecting power of the solution as that it acts as a diluent and permits the removal of tenacious secretion, thereby allowing free drainage. At the suggestion of the author and Dr. Chevalier Jackson, Dr. John A. Kolmer carried out a very interesting series of experiments in animals in bronchial disinfection and immunization.[4] However, the practical results of this experimentation have not as yet been fully determined. It would seem when substances, either chemical, bacteriological or serological, are produced, suitable for use in the lung for sterilization and disinfection, that the best method of application will be through the bronchoscope because the medication can be controlled and restricted to the diseased lobe of the lung. When a considerable quantity of fluid material is introduced into the lung, it should be reaspirated promptly. If it is not aspirated, one should, from the local condition of the lung, be reasonably certain that it would be removed promptly by cough. In the use of iodized oil for pneumonography particular care is used not to force the opaque material into the lung but to allow gravity and the respiratory efforts to carry it in.

As an adjunct to free drainage, all medication that will tend to prohibit the normal cough mechanism should be withheld, particularly opiates and other cough sedatives. The use of atropine is also undesirable because it increases the viscosity of pulmonary secretions and makes it more difficult to expel them from the lung by the cough mechanism.

Dr. William F. Moore, at the Philadelphia General Hospital, has obtained very favorable results from the bronchoscopic intrabronchial application of polyvalent bacteriophage prepared from stock culture.[5] This type of bacteriophage seems at the present to give us the most hope for benefit in the field of intrabronchial medication. The best method of application is by means of the bronchoscope, because the field of application can be limited, its action noted by inspection, and the procedure better controlled.

Contraindications to Bronchoscopy. There are few contraindications to bronchoscopy where there is a positive indication for its use. In every case in which it is possible a careful roentgen-ray examination and a physical examination by a competent internist should be made, prior to bronchoscopic examination.

Modification of Bronchoscopic Technic. In patients urgently dyspneic where there is evidence of bronchial obstruction, as in postoperative pulmonary complications, bilateral atelectasis, acute edema of the lungs such as is seen occasionally post-partum in heart lesions, bronchoscopy may be done for the removal of obstructive secretions without removing the patient from the bed.[6] In a number of instances in a grave emergency of this type, bronchial obstruction has been relieved by bronchoscopic aspiration of secretions. The limit of the use of bronchoscopy where it is indicated, then, must be a matter of the efficiency of the bronchoscopic technic.

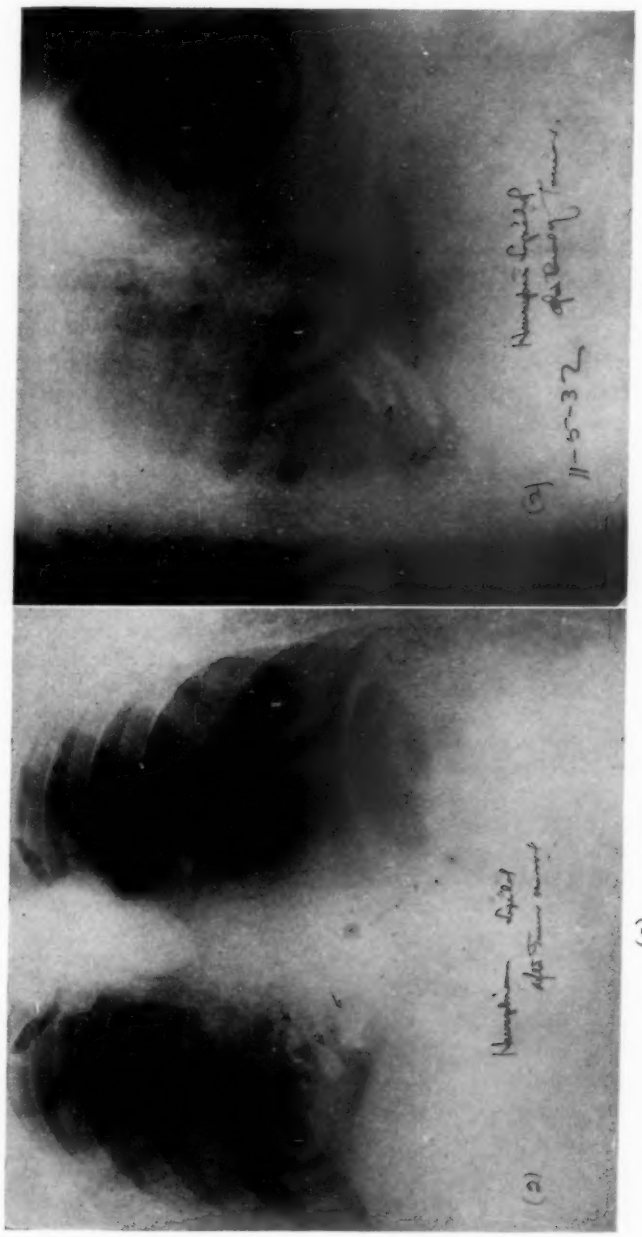
Illustrative cases of the results of bronchoscopic aid in the diagnosis and treatment of conditions which occur frequently in the ordinary run of patients seen by the internist are here presented.

Chronic Cough. Chronic unexplained cough in a patient who has been studied carefully by the usual diagnostic method is frequently encountered. A simple bronchoscopic inspection of the tracheobronchial tree will reveal the cause in many cases and afford a means of treatment that will cure the condition.

Case I

Chronic cough; bronchial obstruction; localized bronchial dilatation.

A male, 45 years of age, an attorney referred by Dr. William MacMurtrie of Philadelphia, had chronic intermittent coughing attacks, more severe at night, over a period of years. The patient was well nourished and not otherwise ill. The strangling cough became so severe that he was unable to follow his occupation. The condition had been variously diagnosed as chronic bronchitis, asthma, etc. Finally the patient's condition became progressively worse and a careful roentgen-ray check-up and physical examination revealed an abnormal density and area of dullness in the posterior portion of the right lower lobe. Bronchoscopic examination revealed a tumor mass blocking the posterior division of the right lower lobe bronchus. The obstructing tissue was removed bronchoscopically and found to be inflammatory tissue, and a localized area of bronchiectasis secondary to the obstruction of the bronchus was demonstrated by lipiodol. (Figure 1.) After removal of the tumor bronchial drainage was restored, the dilated bronchi returned to normal and the patient's symptoms entirely disappeared. The patient has been well three years.



(a) (b)

FIG. 1. Case 1.

Bronchoscopic lipiodol pneumonogram showing the area of bronchial dilatation distal to the location of tumor.
(*a*) Anteroposterior. (*b*) Lateral.
The lipiodol was coughed out. The lung cleared completely after six bronchoscope treatments.

Hemoptysis. Active pulmonary hemorrhage is practically always a contraindication to bronchoscopic examination. Where the condition is not definitely due to tuberculous infection, bronchoscopic examination in the interval between periods of hemoptysis will frequently establish a diagnosis. Overlooked foreign body, carcinoma of the lung, benign tumor of the lung, inflammatory granulation in a bronchiectatic cavity, ulcerative lesion of the bronchus, broncholithiasis, granuloma of the bronchus, pulmonary tuberculosis in which acid-fast organisms had not been demonstrated from sputum examination, each has been established definitely, by bronchoscopic examination, as the cause of hemoptysis.

CASE II

Hemoptysis; overlooked foreign body.

A male, 29 years of age, had had a slight hemorrhage five weeks before admission, a week later a severe hemorrhage, a week following this a third hemorrhage, and three days later a fourth. After several roentgen-ray examinations were made a small dense shadow was detected in the lower lobe of the right lung, near the right border of the heart. In going back over the history it was found that the patient had had extraction of teeth under general anesthesia 15 years and nine years before admission. Following the second tooth extraction there had been a dry cough. The patient's general condition had been otherwise good. The diagnosis of foreign body in the lung was made by Dr. Channing Frothingham of Boston who referred the patient. A special roentgen-ray examination showed that the dense shadow was probably a fragment of a tooth. Bronchoscopy for removal of the foreign body was done under fluoroscopic guidance at the University of Pennsylvania Hospital, after roentgen-ray localization of the tooth by Dr. Pancoast and Dr. Pendergrass, and the foreign body removed. (Figure 2 *a, b, c.*) In order to obtain fluoroscopic guidance it was necessary to use a special method of localization. Opaque markers were placed anteroposteriorly and laterally with the patient in the recumbent position after the method of Dr. Pancoast and Dr. Pendergrass, because the tooth was not dense enough to be seen fluoroscopically although it could be demonstrated very well on a Bucky film. This case illustrates overlooked foreign body as a cause of pulmonary hemorrhage, and also demonstrates the effectiveness of properly guided fluoroscopic bronchoscopic removal of a foreign body that was not sufficiently opaque to be seen on fluoroscopy.

Bronchial Tumors, Benign and Malignant. The diagnosis of bronchial tumor is made certain in a great majority of cases by bronchoscopic examination. Biopsy is possible in many tumors both benign and malignant. Benign tumors may be removed endoscopically while malignant tumors may be treated by radon implantation through the bronchoscope. The secondary pathology, drowned lung, abscess, etc. may be benefited during the irradiation treatment by repeated bronchoscopic aspiration of secretions from the obstructed area of lung. This is especially emphasized by Dr. Eugene Pendergrass who insists on bronchoscopic drainage during the irradiation treatment of his cases of pulmonary tumor. Tumors of the mediastinum and the lung itself may also be diagnosed by bronchoscopy in a percentage of cases.[6] Occasionally a pulmonary tumor may give esopha-

(*a*) (*b*) (*c*)

FIG. 2.

(*a*) Roentgenogram showing tooth shadow at the junction of the diaphragm and heart shadow. Tooth shadow could not be seen fluoroscopically.

(*b*) Roentgenogram showing opaque marker in position. Pancoast-Pendergrass technic. Markers could be seen fluoroscopically and were so placed that they served as guides for the location of the tooth during bronchoscopic removal. The bronchoscopist used the sense of touch as a guide in grasping and withdrawing the tooth.

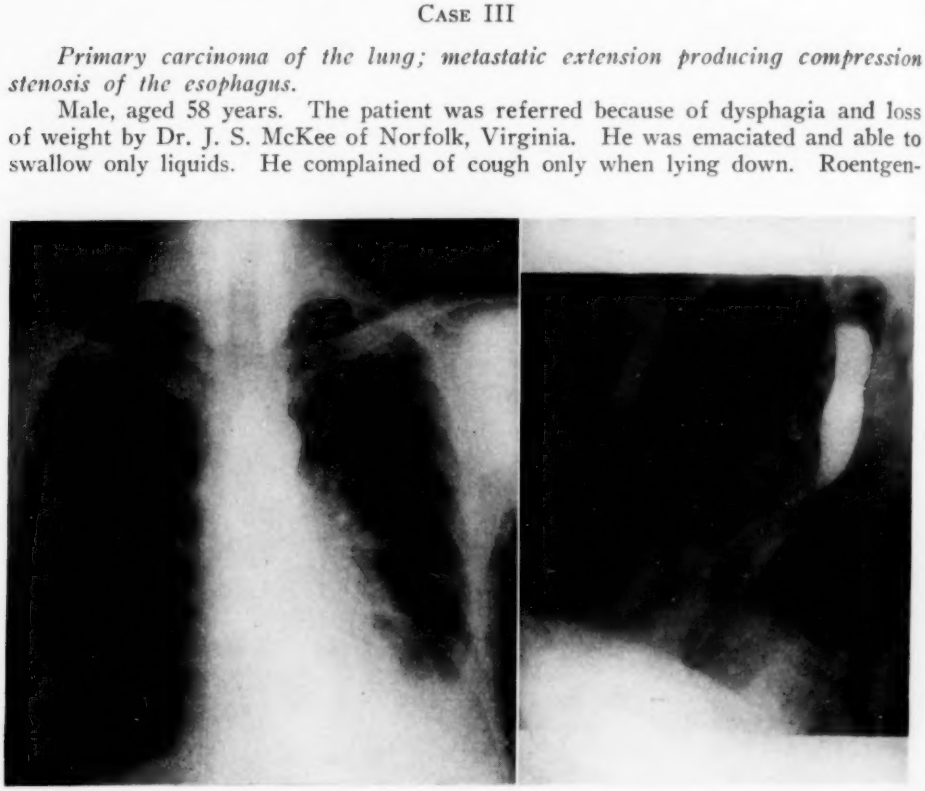
(*c*) Fragment of tooth after removal.

geal symptoms, due to periesophageal extension, and the differential diagnosis can be made only by bronchoscopic examination. (Figure 3.)

Case III

Primary carcinoma of the lung; metastatic extension producing compression stenosis of the esophagus.

Male, aged 58 years. The patient was referred because of dysphagia and loss of weight by Dr. J. S. McKee of Norfolk, Virginia. He was emaciated and able to swallow only liquids. He complained of cough only when lying down. Roentgen-



(*a*) (*b*)

Fig. 3.

(*a*) Roentgenogram showing evidence of peribronchial thickening at the left base. On bronchoscopy, tissue removed from left lower lobe bronchus showed carcinoma.

(*b*) Lateral film, with opaque mixture, shows stenosis of the lower esophagus. Esophagoscopy showed compression, no ulceration. The triangular area in front of the shadow of the lower esophagus represents atelectasis due to bronchial occlusion by the cancer in the left lower lobe.

ray examination showed a stenosis of the esophagus involving the lower third, evidence of an old tuberculous lesion in the apices of both lungs, and increase in density at the left base, the suggestion being that this might be due to a bronchiectasis. The esophagoscopic examination revealed an annular stenosis involving the lower third of the esophagus, and on passing a small esophagoscope in the strictured area the mucous membrane was found to be smooth, the lesion apparently being periesophageal, with no ulceration.

Because of the roentgen-ray evidence of a lesion in the left lower lobe, bronchoscopic examination was made which showed an organic stenosis of the left lower lobe bronchus with firm infiltration and ulceration of the bronchial wall. Histologic diagnosis by Dr. E. A. Case was "bronchial carcinoma," from bronchoscopic biopsy. The bronchoscopic finding in this case enabled us to make a diagnosis of primary

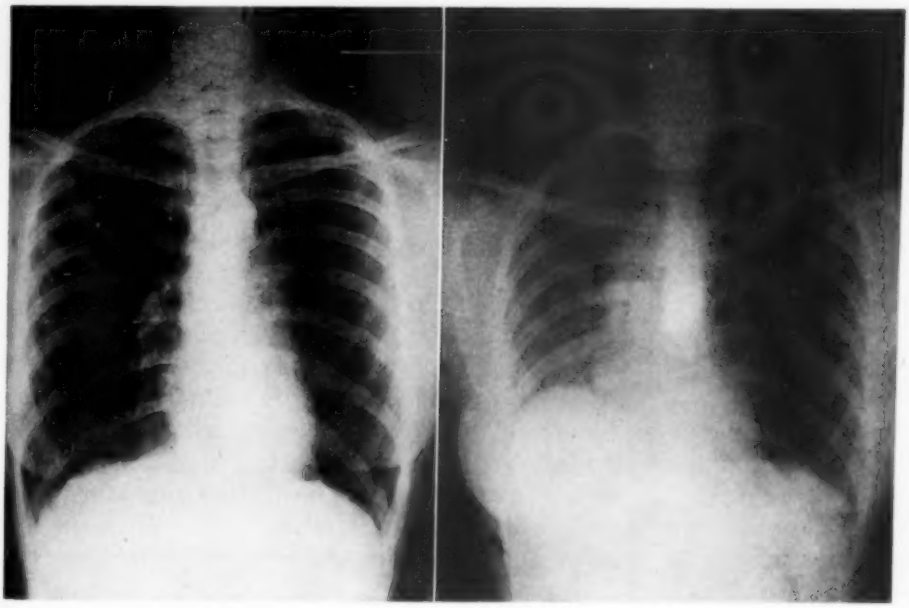
carcinoma of the bronchus with periesophageal extension producing compression stenosis of the esophagus. These findings were confirmed later in this patient by autopsy.

Tuberculosis. In the ordinary case of uncomplicated pulmonary tuberculosis with a positive sputum there is no indication for bronchoscopy. In suspected cases where the sputum is negative, bronchoscopically removed secretion from the involved area of lung frequently shows tubercle bacilli and confirms the diagnosis. The presence of a tuberculous infection is not a contraindication to bronchoscopic examination. A persistent wheeze, obstructive emphysema, obstructive atelectasis or drowned lung are indications for bronchoscopy.

Case IV

Pulmonary tuberculosis; bronchial stenosis.

Female, aged 40, referred by Dr. Frank Burge of Philadelphia because of a persistent expiratory wheeze and evidence of emphysema of the left lung. Dr. Burge had made a diagnosis of tuberculosis in this patient, had placed her in a sanatorium and, with pneumothorax treatment, had arrested the disease. The patient had gained weight to above normal, and the sputum was free of tubercle bacilli. Physical ex-



(*a*) (*b*)

Fig. 4. Case 4.

(*a*) Anteroposterior chest film, taken on inspiration, showing the heart in normal position.

(*b*) Anteroposterior film on expiration showing displacement of the heart to the right, marked depression of the left diaphragm, the characteristic findings of obstructive emphysema.

Bronchoscopic examination showed the obstruction to be due to tuberculous granulation tissue obstructing the left main bronchus.

amination gave evidence of bronchial stenosis and roentgen-ray examination showed marked obstructive emphysema of the left lung. Bronchoscopic examination revealed fungating masses of tissue in left main bronchus which obstructed the airway to such an extent that the left bronchus was almost completely blocked on expiration. The tissue masses were removed bronchoscopically and the tissue, examined by Dr. E. A. Case, was reported as showing "chronic exudate and tissue the seat of tuberculosis."

Removal of the masses relieved the bronchial obstruction to a considerable extent and so far there is no evidence of recurrence of this type of tissue. There is, however, evidence of stenosis of the left main bronchus which has been relieved by bronchoscopic dilatation. A full report of this case will be made subsequently by Dr. Burge.

Suppurative Disease of the Lung. In every patient with suppurative lesion of the lung, unless it is one in which there is pleural involvement with urgent demand for external surgery, bronchoscopic investigation as an aid to diagnosis and localization of the lesion should be carried out.

Bronchiectasis. Bronchoscopic examination will reveal the condition of the interior of the larger bronchi. Aspiration of secretion and bronchoscopic pneumonography will best demonstrate the extent of the lesion. If bronchial obstruction can be relieved by intrabronchial treatment the function of the diseased area of lung may be restored. If no improvement results the information obtained by the study will be of aid to the surgeon in classifying the condition for surgical treatment, that is, it will help to decide whether the patient has a "first, second or third degree bronchiectasis."[8] In advanced bronchiectasis, bronchoscopy is palliative only, and if surgery is not done, bronchoscopic treatment combined with postural drainage and medical care will make the patient's burden easier. Every case of bronchiectasis should have careful bronchoscopic study before the diseased area of lung is excised.

Prevention of Bronchiectasis by Bronchoscopy. There is much controversy regarding the exact etiology of bronchiectasis. There is, however, a factor which has been emphasized little except by Chevalier Jackson, namely, localized infection of the lung, with obstruction to the normal bronchial drainage. There are a number of pathological conditions which are undoubtedly followed by bronchiectasis in which, if normal drainage is restored and maintained by way of the tracheobronchial tree, bronchiectasis will be prevented. Of these conditions may be mentioned unresolved pneumonia, purulent tracheobronchitis, localized infection with obstruction and drowned lung, pulmonary changes following the sojourn of foreign body.

CASE V

Unresolved pneumonia.

Female, colored, aged 25, referred from the service of Dr. George M. Piersol, Graduate Hospital, University of Pennsylvania. This patient had developed an extensive lesion in the right chest which had been under observation for a period of six weeks. The course of the disease was at first typical of pneumonia, her temperature then became septic, and the lesion extended until it involved the entire right lung. Her general condition remained about the same. (Figure 5.) The lung

failed to clear and she was referred for bronchoscopic examination. Following the first bronchoscopy there was very profuse expectoration of foul pus. A second bronchoscopy was done three days later. Her temperature then remained normal; the quantity of pus expectorated gradually lessened. Four bronchoscopic treatments in all were given. Her condition improved to such an extent that she was dis-

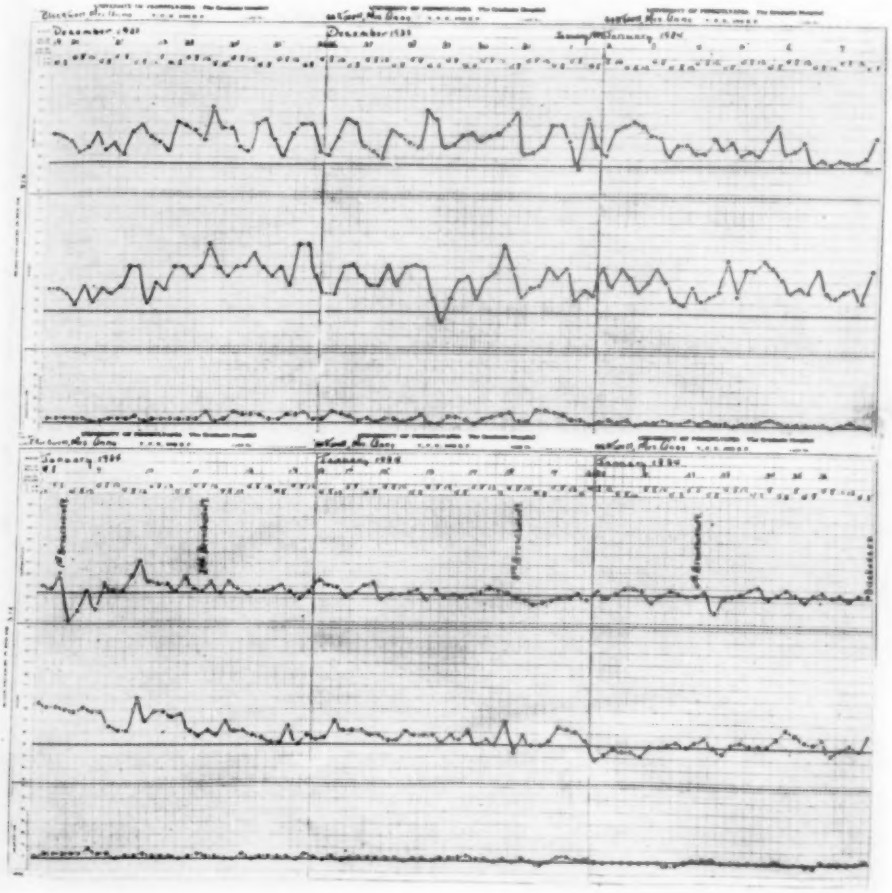


FIG. 5. Clinical chart showing the course before, during and following bronchoscopic treatment.

charged from the hospital after two weeks' treatment. She has been kept under observation as an out-patient for a period of six months and her lung is entirely clear. (Figure 6.)

Postoperative Pulmonary Complications. Postoperative pulmonary complications, in many cases, require bronchoscopic examination as a means of differential diagnosis to exclude aspiration infection or foreign body. Bronchoscopy should be done early as a diagnostic examination and it will

very frequently promote drainage to such an extent that prompt resolution of the condition will occur.

In massive collapse where other measures do not promptly restore the lungs to normal, bronchoscopic aspiration will open the airway and restore ventilation and drainage. One of the most important factors in the production of postoperative pulmonary atelectasis is impairment of the cough

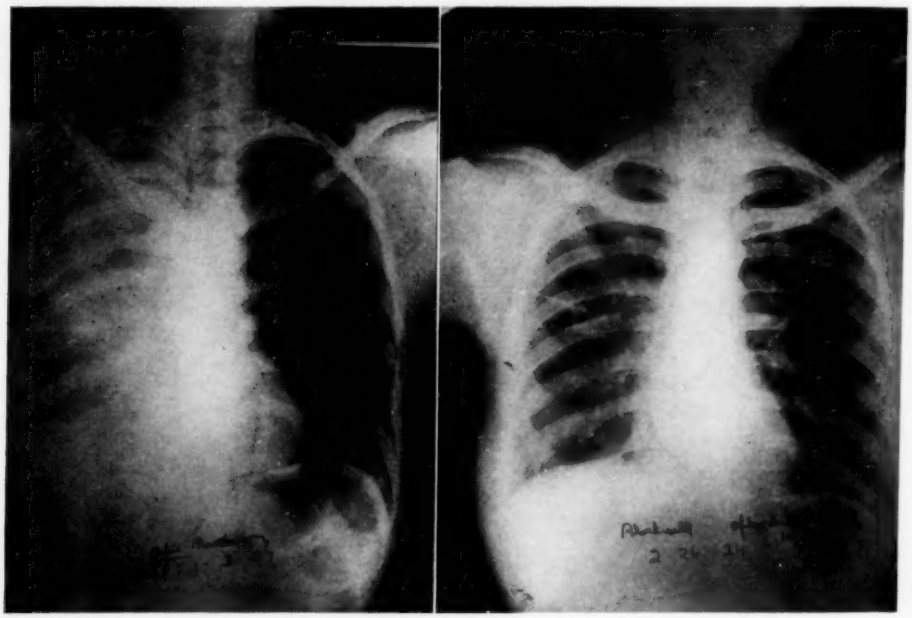


FIG. 6. Roentgenogram showing the chest condition before bronchoscopic examination and after bronchoscopic cure.

mechanism as the result of operative procedure. In these cases bronchoscopy may be required to supplement the coughing efforts in the removal of obstructive secretions.[7]

CASE VI

Postpartum edema of the lungs.

A woman, 35 years of age, was referred by Dr. Arthur First of Philadelphia. She had been delivered of a normal child at term without instrumentation. The patient had a mitral stenosis, well compensated. Within 24 hours she developed an acute edema of the lungs although her heart condition was pronounced by Dr. Henry Smookler to be satisfactory. When seen in consultation she was propped up on a back rest. The tracheobronchial tree was rapidly filling with secretion which she was unable to remove by coughing efforts. The medical consultant assured us that her heart condition warranted bronchoscopic aspiration. A modified bronchoscopic technic was used without removal of the patient from bed. About 150 c.c. of thin brownish secretion were aspirated from the tracheobronchial tree. Dyspnea was immediately relieved, there was no recurrence of the pulmonary edema, and the patient progressed to an uneventful recovery. (Figure 7.)

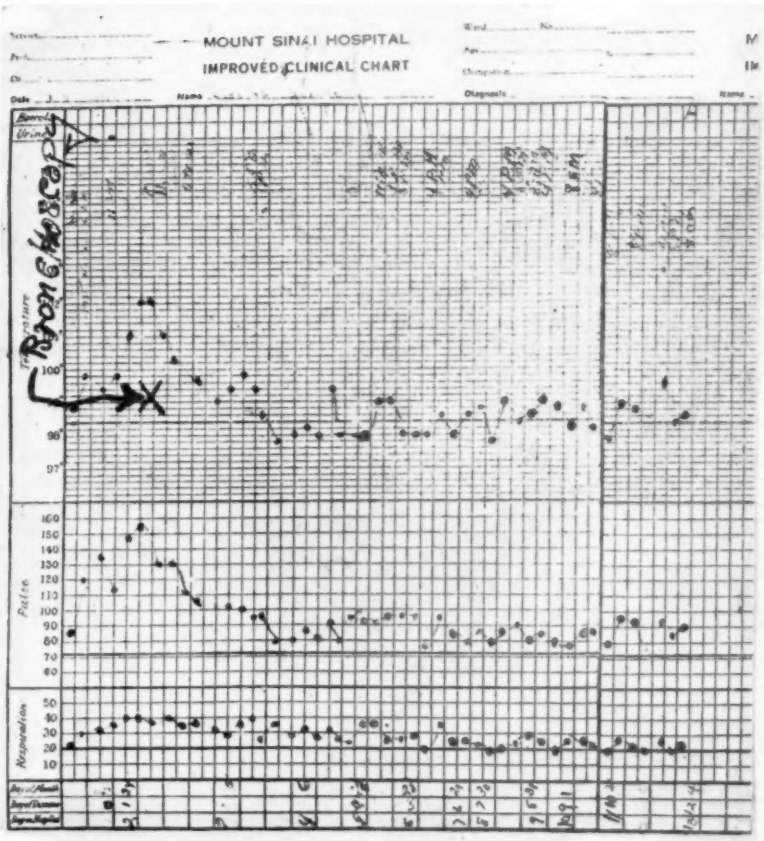


FIG. 7. Clinical chart showing patient's condition at and subsequent to bronchoscopic removal of obstruction.

CONCLUSIONS

1. Due to the perfection of instrumentarium and of the method of bronchoscopic procedure without general anesthesia, bronchoscopy has reached a point in development where it is invaluable as an aid in the diagnosis and treatment of pulmonary disease.

2. The bronchoscopic findings will supplement all other methods of examination in pulmonary disease. In order to obtain the best results, special training and continuous practice by the bronchoscopist is required, together with a trained personnel, adequate instrumentarium and the support and close coöperation of the internist, the roentgenologist and the surgeon.

3. Modern bronchoscopy has developed a world-wide interest because of its efficiency as an aid in the diagnosis and treatment of pulmonary disease. Its continued advance and development will depend upon the interest and support given by the internist and the pediatrician who see the patients first and who decide whether or not the patients shall have the benefit of bronchoscopic consultation.

BIBLIOGRAPHY

1. Tucker, G.: An infant bronchoscope, Trans. Section on Laryngology, Otology and Rhinology, Am. Med. Assoc., 1932.
2. Pancoast, H. K., Pendergrass, E. P., and Tucker, G.: Localization of foreign bodies in lung by roentgen examination with comments on bronchoscopy under biplane roentgenoscopic guidance, Am. Jr. Roentgenol. and Rad. Therapy, 1932, xxvii, 225–233.
3. Tucker, G.: Bronchoscopic observations on obstructive pulmonary atelectasis, Arch. Otolaryng., 1931, xiii, 315–325.
4. Kolmer, J. A.: Broncho-pulmonary immunization and disinfection, Proc. Am. Laryng. Assoc., 1933.
5. Moore, W. F.: Personal communication.
6. Pendergrass, E.: Personal communication.
7. Tucker, G.: Postoperative pulmonary complications, bronchoscopic aid in diagnosis and treatment, Proc. Section on Surgery, Am. Med. Assoc., 1933.
8. Archibald, E.: The consideration of the dangers of lobectomy in relation to the technic of the operation, Proc. Am. Assoc. Thorac. Surg., 1934.

THE IMPORTANCE OF ACTUALLY MEASURING THE TOTAL HEAT PRODUCTION *

By L. H. NEWBURGH, *Ann Arbor, Michigan*

A KNOWLEDGE of the basal metabolism is informative in many different problems. Its diagnostic value is quite familiar; but its use as a basis for estimating the total production of heat is open to errors which are sometimes so large that the observer is seriously misled.

In the pursuit of our own studies, it became of paramount importance to be possessed of a means of knowing accurately how much energy was dissipated day after day so that we could compare the inflow of calories with their expenditure. This we were able to do by the development of Benedict's [1] study of the insensible perspiration. Time does not permit a discussion of the method. It is described in detail in our publications.[2] Suffice it to say here that it is capable of yielding extremely accurate data when the proper precautions are followed.

The earlier way of estimating the total heat production consisted of adding to the basal metabolism, theoretical increments appropriate for the activity of the subject.

In 1918, as a war measure, Lusk [3] made such prediction tables. The average weight of thousands of individuals of a given height at 35 years of age, was calculated. The normal basal metabolism was then figured by means of the DuBois height-weight formula. To these basal values, 10 per cent for 16 hours was added to provide for sitting and standing. Tables for the extra calories per hour attributable to various occupations were then consulted and the values for an eight hour day corresponding to the occupation were added to the sum already obtained. A final increment of 200 calories for men and 150 calories for women was included to account for small movements such as dressing. Part of the information may be seen in table 1. The theoretical basal metabolism was 1700 calories for 24 hours.

TABLE I

Predicted Increment Corresponding to Activity: Per cent of Basal	Total	Type of Activity
6	1800	Bed
40	2375	Tailor
60	2730	Shoemaker
94	3300	Carpenter
160	4400	Stone Mason
196	5025	Woodsman

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934.

It must be remembered that these predictions were theoretical and that no test of their accuracy was made. The first three values are strikingly low. It is especially difficult to accept the statement that the patient in bed expends only 100 calories beyond the basal. Most writers have assumed that 20 to 30 per cent needed to be added to the basal metabolism to arrive at the total expenditure of energy for persons in bed. It requires only a moment's thought, however, to make one realize that the variations from patient to patient must be large. It seems unlikely that any general prediction for this group of persons can have much value.

We have applied our method for measuring total heat production to three youths who had been in bed for some months because of minimal tuberculosis of the lungs. All were afebrile and entirely free of symptoms. It might be supposed that their long experience in bed had taught them to be reposeful. The facts revealed by actual measurement came as a great surprise to us.

TABLE II

Basal and Total Production of Heat by Boys Continuously in Bed

Patient	Basal Metabolism Cal. for 24 Hours	Total Metabolism Cal. for 24 Hours	Total Metabolism Increment in per cent of basal
E. P. age 18	1550	2558	65
C. S. age 15	1550	2325	50
H. J. age 18	1580	2350	49

Nor were the total calories increased when these patients were permitted the freedom of the room.

We had a similar experience with a normal subject who was first in bed for a week and was then allowed to move freely about the room during the second week. These experiences give rise to the question whether anything is gained by forcing patients to remain continuously in bed when they do not feel ill enough to stay there voluntarily. Perhaps they would often expend less energy if they were permitted to make themselves comfortable within the confines of a large and pleasant room.

We have also recorded the heat production of a series of men and women while they were pursuing their usual modes of life. Table 3 contains the data. The increment of expenditure of energy varies from 53 to 120 per cent. Leaving out the last subject, it is noteworthy that a group of young people, none of whom was earning his livelihood by manual labor, expended an amount of energy roughly equal to their basal metabolism as a result of the day's activities. Examination of the individual values should convince the reader that a prediction of the total heat production for any one of the subjects would be liable to a large error.

We have determined the total dissipation of energy by obese persons and compared these values with the calories of the diet. We have then predicted

TABLE III

Total Energy Metabolism for Various Activities

Sex	Age	Wt. Kg.	Ht. Cm.	Basal Metabolism Cal. for 24 Hours	Total Metabolism		Occupation
					Cal. for 24 Hours	Increment in per cent of basal	
M.	24	61	180	1490	2586	73	Student of architecture
F.	35	53	154	1150	2075	80	Nurse in charge of clinic
M.	30	56	174	1561	2975	90	Intern
M.	28	57	183	1452	2920	101	Laboratory worker
F.	24	73	168	1633	3210	96	Laboratory worker
M.	25	67	175	1691	3425	102	Medical student
M.	23	64	165	1623	3570	120	Graduate student in chemistry
M.	24	66	174	1685	3550	111	Graduate student in chemistry
M.	56	70	180	1630	2500	53	Retired; sedentary habits

the loss of weight and in that way we have convinced ourselves that all obese persons will lose weight when they are underfed; and what is more important, that these individuals have invariably become fat simply and solely because they have eaten too much.

We have recently had the opportunity of studying a patient of the type described by Cushing. The outstanding characteristics are uniform decalcification of the skeleton and adiposity of the upper half of the body. Figure 1 shows the patient, 19 years old, who is only 5 feet tall, when he weighed 180 pounds. You will note that his legs and arms are not at all fat but that he appears to possess a huge deposit of adipose tissue in the chest and abdomen. This apparent localization of the fat lends an air of mystery to the situation and is generally interpreted as evidence that the gain in weight is not merely due to overeating. The baneful intervention of an endocrine gland is suspected. After this patient had lost 50 pounds in response to a diet of about 900 calories, photographs were made again (figure 2). This time the weight of 132 pounds is normal and still the chest and abdomen are as protuberant as they were in the beginning. Examinations by the roentgen-ray (figure 3) show that the spine is unusually short and hence much less than the normal space was provided for the organs. The necessary room has been obtained by an upward and outward movement of the ribs. What superficially appears to be a localized accumulation of adipose tissue is in fact merely the configuration of a deformed skeleton. As further evidence that there is nothing peculiar about the obesity of this patient, attention is called to figure 4. The solid line represents the actual loss of weight in response to underfeeding. The broken line indicates the predicted decline in weight calculated from the difference between the total expenditure of energy and the calories of the diet. It is difficult

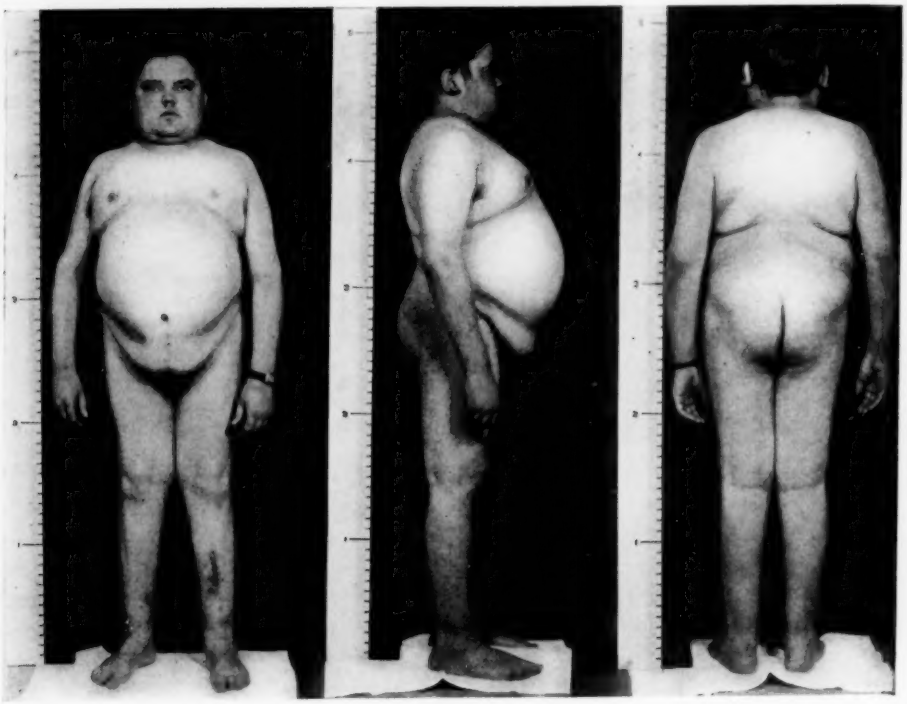


FIG. 1

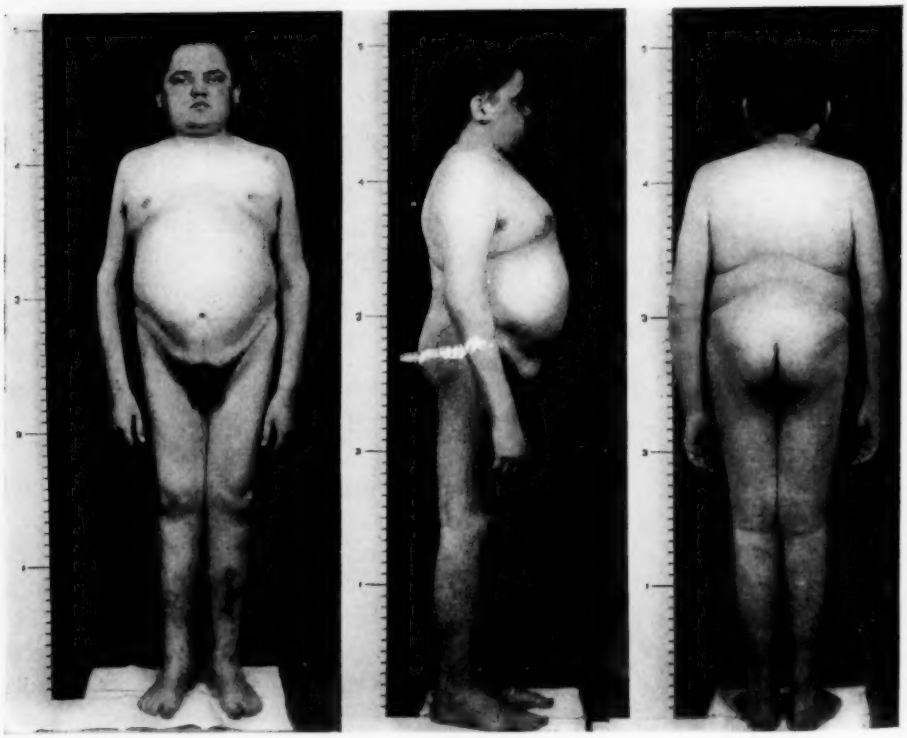


FIG. 2

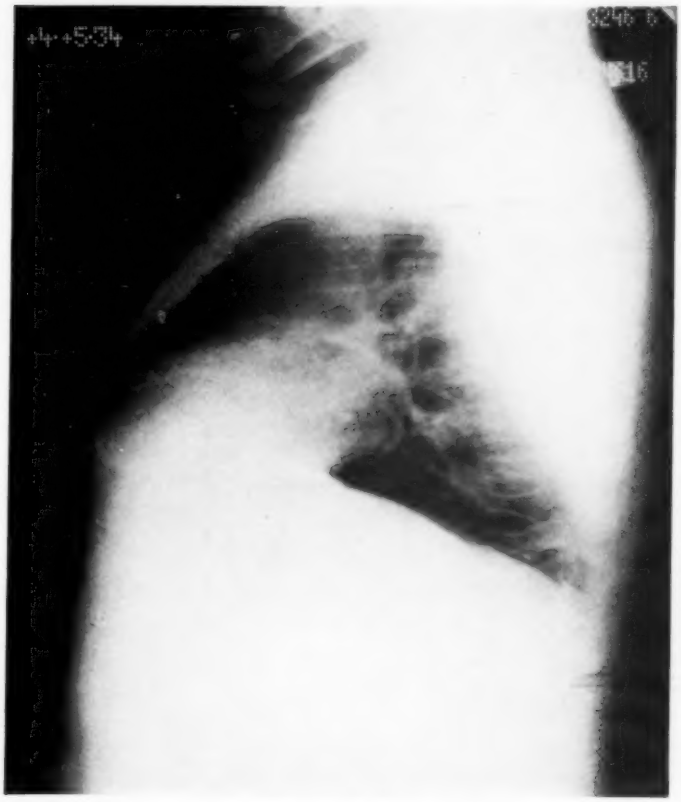


FIG. 3

to believe that an individual, whose weight during a period of 54 days was reduced by underfeeding to within 22 grams of the predicted value, could have become fat for any reason other than overeating.

The next patient is interesting because of the dramatic response to undernutrition. He exhibited enormous localizations of adipose tissue and his initial weight of 560 pounds was astoundingly great. Both features are often credited with being signs of endogenous obesity. His appearance at the beginning of treatment is shown in figure 5. During the ensuing year his diet afforded him 300 calories a day. This effected a loss of weight of 287 pounds (figure 6). During the second year he received 600 calories daily and lost 93 more pounds. He now weighed 194 pounds, a weight that was considered satisfactory for his height. He was now told to keep his weight stationary by judicious selection of his food. How well he succeeded is shown in figure 7, taken nine months after he had been told that he had lost a sufficient amount of weight, since he weighed the same amount.

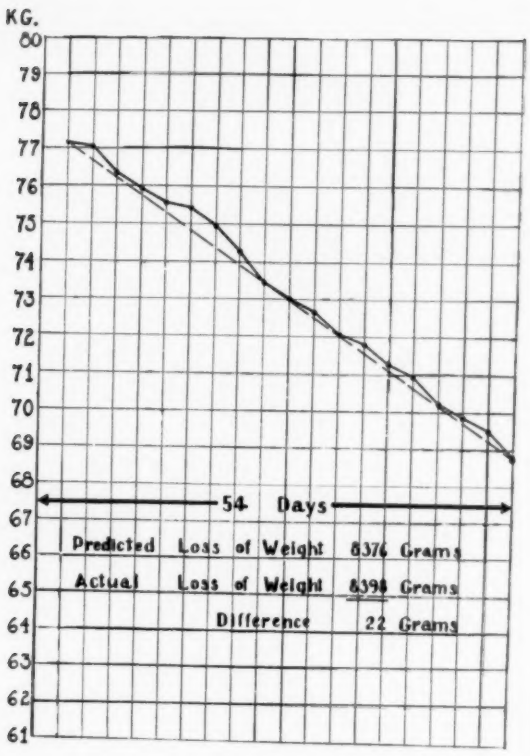


FIG. 4

Grafe,[4] in his book published within the year, states that obese individuals who maintain their weight for a period of time in spite of underfeeding, are victims of endogenous obesity. If this were true, the responses portrayed in figure 8 could not have occurred. This adipose female who was in bed throughout the study expended close to 2500 calories daily. When her diet contained that number of calories, she neither gained nor lost weight (first period). She next received about 1800 calories from a diet high in carbohydrate—260 grams daily. She responded by a steady loss of weight (solid line) that corresponded with the predicted loss (broken line). In the final period she also received about 1800 calories but now the diet contained little carbohydrate and much fat. This caused an initial precipitous loss followed by a period during which she did not lose weight. Since both types of response were produced in the same individual by manipulation of the diet, I think you will agree that the manner in which the weight responds to dietary treatment is not determined by something within the individual but rather by the character of the diet.

Furthermore, this ability to maintain the weight in the face of underfeeding is not the sole possession of obese persons since we have reproduced

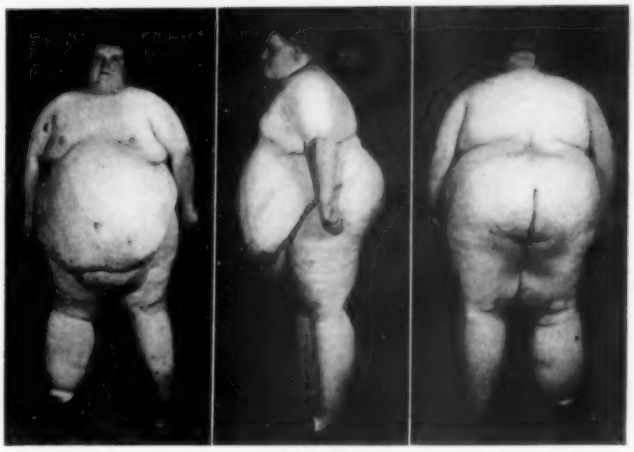


FIG. 5

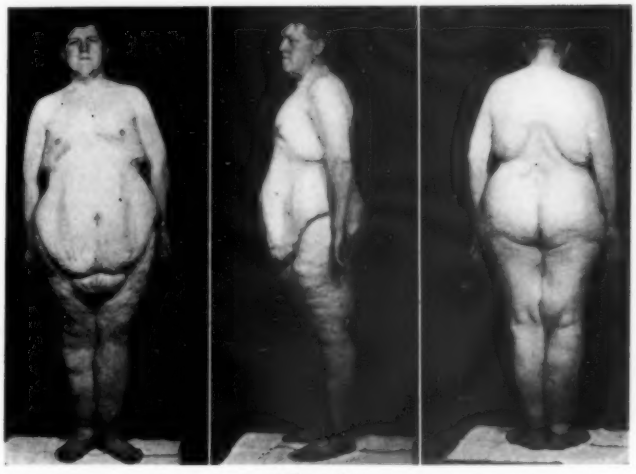


FIG. 6

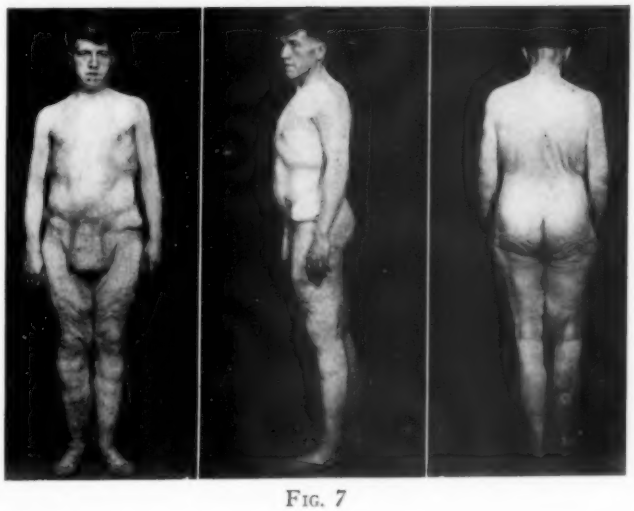


FIG. 7

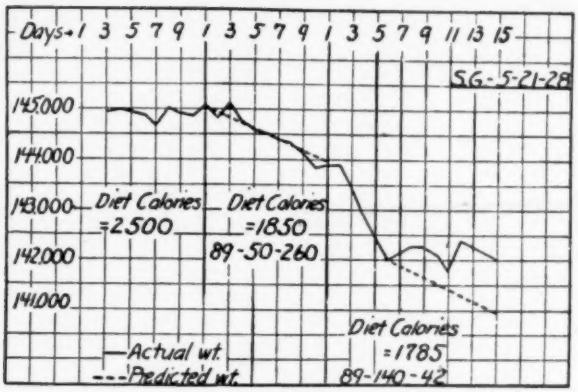


FIG. 8

it in the normal as may be seen in figure 9. This normal man who was in bed throughout the study, received 1078 calories daily in the form of 69 grams of protein, 91 grams of fat and 148 grams of carbohydrate. He

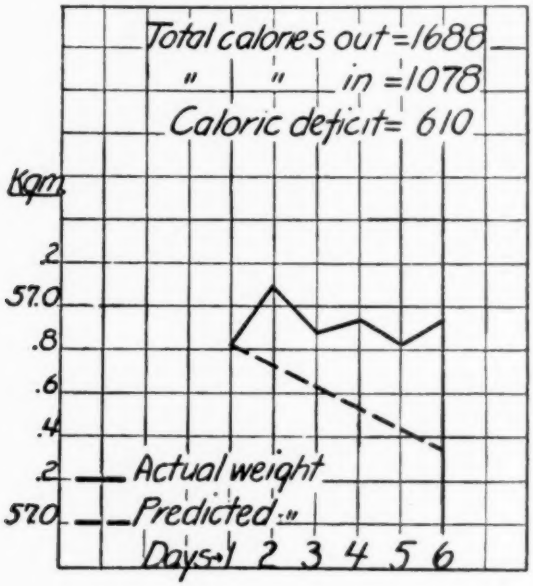


FIG. 9

dissipated 1688 calories a day. The diagram shows a period of five days during which he destroyed 475 grams of bodily tissue. Nevertheless he gained 115 grams of weight in these five days. Clearly a phenomenon displayed by a normal man cannot be classed as a specific sign of disease.

REFERENCES

1. Benedict, F. G., and Root, H. F.: Insensible perspiration; its relation to human physiology and pathology, Arch. Int. Med., 1926, xxxviii, 1–35.
2. Newburgh, L. H., Wiley, F. H., and Lashmet, F. H.: Method for determination of heat production over long periods of time, Jr. Clin. Invest., 1931, x, 703–721.
3. Lusk, G.: The elements of the science of nutrition, 4 Ed., 1928, W. B. Saunders, Philadelphia, page 465.
4. Grafe, E.: Metabolic diseases and their treatment, 1933, Lea and Febiger, Philadelphia.
5. Newburgh, L. H., and Johnston, M. W.: Nature of obesity, Jr. Clin. Invest., 1930, viii, 197–213.

CERTAIN ASPECTS OF PULMONARY ABSCESS FROM AN ANALYSIS OF 210 CASES *

By Donald S. King, M.D., F.A.C.P., and Frederick T. Lord, M.D., F.A.C.P., *Boston, Massachusetts*

Certain aspects of pulmonary abscess are presented as a continuation of the study of this disease at the Massachusetts General Hospital. Two hundred and twenty-seven cases occurring between 1909 and 1924 have been analyzed by one of us.[1, 2] The present series embraces 211 cases observed from 1924 to 1932. As of this number all but one has been followed to the termination in death or present condition from two to nine years after discharge, the discussion to follow is based on the 210 cases. For the unusual success in the follow-up we are indebted to Miss Eleanore A. Lewis and Mrs. Alice R. Coghlin.

Though the cases under discussion are all classed as lung abscess, the designation lung gangrene would be equally appropriate for the great majority of the series, inasmuch as in 192 cases the sputum is recorded as foul. No note as to the odor is recorded in 14 and the sputum was said not to be foul in four. There was no sputum in one case in which abscess was found at autopsy.

Predisposing Factors

The etiologic importance of operations about the upper respiratory tract has increased. While one out of every three cases of abscess could be traced to such a procedure in the 227 cases occurring between 1909 and 1924, the proportion in the present series has risen to about one in two cases (117 of 210 cases, or 55.7 per cent). The operative procedures included the removal of tonsils and adenoids in 81 (38.6 per cent), the extraction of teeth in 26 (12.4 per cent) and an upper respiratory operation in 10 (4.8 per cent). The increase in the proportion of cases which follow operations about the upper respiratory tract may be ascribed to the more frequent performance of such operations in recent years. There are, in addition, 19 (9.0 per cent) due to other operations under a general anesthetic, making a total of 136 (64.7 per cent) referable to a previous surgical procedure. The etiologic factors in the remaining 74 (35.2 per cent) are less clear. In 48 (22.9 per cent) the onset was insidious and the cause undetermined. A more stormy onset in 17 (8.1 per cent) suggested pneumonia as a cause, but the evolution and grouping of initial symptoms were consistent with lobar pneumonia in only three instances. The abscess followed an upper respiratory infection in 5 (2.4 per cent).

In this series, 141 (67.1 per cent), or two out of every three cases, occurred under such circumstances as to make it reasonable to assume that

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934.

the abscess arose in consequence of access to the lung of infected material from the upper respiratory tract.

Special Diagnostic Measures

Bronchoscopy. Examination by this means should be considered in all cases with localized pulmonary suppuration. It is especially indicated when there is evidence of bronchostenosis for the purpose of establishing the presence or absence of a foreign body or tumor. Bronchoscopy was done on 72 cases in the present series. Inflammatory narrowing of a bronchus was thus established in 29 and a congested mucous membrane in 11. It is helpful in certain cases in more accurately localizing the abscess by the determination of the part of the bronchial tree from which pus emerges, but the expulsion of purulent material from one bronchus to another by cough may make it difficult to determine its source. In our experience, the method has not proved of value in the treatment of lung abscess in the absence of foreign body as a cause.

Lipiodol Insufflation. Seventeen cases were investigated by means of lipiodol insufflation for the purpose of more accurate localization of the abscess. The number is small, as the site of the process can ordinarily be satisfactorily determined by other means. In nine of the cases, or about one-half, additional information of value was not obtained. There is, however, a small group of cases in which localization by roentgen-ray is uncertain on account of obscuration by the overlying shadow of the heart or the diaphragm. With improvement in roentgen-ray technic and the use of profile films in addition to anteroposterior views, lipiodol is seldom necessary for the localization of lung abscess. It is, however, of great value in the differentiation of lung abscess from bronchiectasis.

Prognosis

Of the 210 cases, 73 (34.8 per cent) completely recovered, in 49 (23.3 per cent) the condition was improved, in 10 (4.7 per cent) the disturbance persists unabated, and 78 (37.1 per cent) died. Of 96 operated cases, 27 (28.1 per cent) recovered, 26 (27.1 per cent) improved, 5 (5.2 per cent) were unimproved and 38 (39.5 per cent) died. Of the 38 deaths following operation, we estimate that in 12 the fatalities were in part at least to be ascribed to the operative interference.

Treatment of Lung Abscess

From our review of the present series, certain comments may be made regarding the treatment. In making a decision regarding the most desirable course to pursue, it should be appreciated that there is a large group of cases in which the indications are on the borderline between conservative measures and surgical interference.

Conservative Treatment. It is, in general, best to subject patients with lung abscess to a period of observation and investigation for the purpose of deciding upon the best course to pursue. In adopting an expectant policy and meanwhile using bed rest and postural drainage, it must be kept in mind that there is danger of extension of the suppurative process, of the development of multiple from a single focus, of empyema, of cerebral abscess and of septicemia. But in view of the hazards of surgery and the chance of recovery without radical measures, it, nevertheless, seems desirable first to give a fair trial to the simpler procedures. This régime is, in general, applicable only within the first two to three months of the illness and should be continued only so long as progress is favorable, as indicated by the amount and character of the sputum, the abatement of the toxemia and a diminution of the extent of the process by physical and roentgen-ray examination.

Recovery without Radical Treatment. From previous experience, the chance of recovery without resort to operation was estimated at about one in every 10 cases.

In the present series the number of recoveries without resort to pneumothorax or surgery has risen to a considerably higher proportion. Forty-five (21.4 per cent) of the 210 were completely relieved of all indications of abscess. In addition, in seven the returns indicate restoration to health and capacity, but the presence of cough and scanty expectoration without foul odor, make it necessary to place them in a doubtful class. The expectation of relief may thus be estimated for the present series as about one in every five cases.

Information is desirable regarding the factors which may be expected to favor recovery without resort to radical measures and it is, in consequence, of interest to consider this recovered group more in detail, with respect to the (1) exciting causes, (2) previous duration and (3) site of the process.

The exciting causes in the 45 completely recovered cases were: the removal of tonsils and adenoids in 21 (46.7 per cent); the extraction of teeth in seven (15.6 per cent); an upper respiratory operation in three (6.6 per cent); other operation under a general anesthetic in four (8.9 per cent); an upper respiratory infection in one (2.2 per cent); and pneumonia in two (4.4 per cent). The abscess was primary in seven (15.6 per cent). The percentage incidences of the various exciting causes correspond so closely in the recovered group and in the series as a whole that the nature of the exciting cause appears not to be of moment in influencing recovery without interference.

A short previous duration is one of the most important factors in favorably modifying the chance of recovery under medical observation. In considering the prospect of recovery in relation to a duration of two months or less in the series as a whole, we find that of 110 cases in this category, 34 (30.9 per cent), or about one in every three cases, recovered without other than conservative treatment. Though the expectation of recovery

without operation is thus largely confined to patients with a short previous duration of the disease, 11 cases recovered after a longer period of illness, including five cases of two to three months', one of four months', one of six and one-half months', three of 11 to 12 months' and one of 18 months' duration. The prospect of spontaneous recovery after a long previous duration is more favorable than analysis of the earlier series seemed to indicate, as in that series none of the cases with a previous duration longer than nine weeks recovered spontaneously.

The site of the process is of moment to the prospect for recovery without interference; and in this as in the previous series, a location at or above the root of the lung is relatively favorable, while lesions below this level are less promising. In general, also, it may be said that the symptoms due to the infection and the extent of the pulmonary process were less marked in the cases recovering without radical measures.

Neoarsphenamine in Treatment. In view of the frequency with which neoarsphenamine is used in the treatment of lung abscess or gangrene, it is desirable to obtain more definite information regarding its merits. Fifty-five patients in the series have been treated with neoarsphenamine. Comparison of the results in this group with those in the series as a whole suggests that no favorable effect is to be ascribed to its use. Estimate of the value, if any, of the drug is complicated in a majority of the cases by the variability and, at times, by the length of the previous duration of the condition, before treatment was begun. There are, however, seven cases treated with three or more doses of neoarsphenamine within 13 to 21 days of the onset of the disease. Of these seven cases, two recovered completely and one died under medical care. Two of the remaining four were later subjected to pneumothorax and two to a rib resection and drainage. In the last two mentioned cases, in spite of the institution of treatment in one within 16 days, in the second within three weeks after onset, there was extension of the process by roentgen-ray before operation was done. Neither in the clinical aspects nor in the final results, is there evidence that the administration of neoarsphenamine favorably modified the course of the disease.

Collapse Therapy

Brilliant results in the application of collapse therapy to the treatment of pulmonary tuberculosis merited the hope of its successful use in the management of lung abscess. The suppurative lesions differ, however, in that drainage is the essential factor in healing, while rest is of paramount importance in recovery from tuberculosis.

Pneumothorax in Treatment. Treatment by artificial pneumothorax was attempted in 22 patients, but failed in six because of adhesions. Partial collapse was obtained in four and complete collapse in 12. Of these 16 cases nine may be regarded as failures so far as this method of treatment is concerned, as the patients later came to operation. Of the remaining seven,

one completely recovered, three improved and three died. Thus, in our experience, there are only four cases in which benefit was apparently derived from the treatment and the advantage in this small group is offset by three patients in whom the procedure was certainly or probably harmful. All three developed empyema under the treatment and of the three, two died. Though empyema occasionally complicates untreated abscess, its occurrence after artificial pneumothorax in three of 16 cases suggests that the procedure was largely responsible. In our four favorable cases, improvement or complete recovery might have taken place without resort to artificial pneumothorax. In rare instances, as in one case in the series, the artificial pneumothorax makes it possible to localize an abscess, the site of which is otherwise uncertain.

Artificial pneumothorax has proved disappointing as a therapeutic measure. Its use entails the danger of empyema, which may in turn make surgical measures difficult or impossible.

Phrenic Nerve Operation. The induction of diaphragmatic paralysis has been followed by recovery in isolated instances of lung abscess. The procedure would seem theoretically likely to be most serviceable with a lesion at the base, but there is always the possibility that bronchial drainage will be hindered rather than favored by this method. It was used as the sole surgical measure in only two cases in this series. In one instance, a man of 34, with a history of cough and foul sputum amounting to 12 to 15 ounces daily for a year, and a process at the right base, the patient died of hemorrhage about six weeks after the crushing of the right phrenic nerve. In the second case, a man of 58, with an abscess involving the middle and right upper lobes, there was no improvement following a right phrenic nerve operation and the patient committed suicide one and one-half years later.

Thoracoplasty. Thoracoplastic collapse therapy may be considered with multiple, diffuse, unilobar or unilateral abscesses of such a previous duration that spontaneous recovery cannot be expected. In adopting this method, it is desirable to exclude cases in which there is a prospect of complete recovery following open drainage or lobectomy. Thoracoplasty has the merit of a relatively low operative mortality and the disadvantage that by this means alleviation rather than cure may be expected. Of 15 cases subjected to thoracoplasty, in three a complete posterior operation was done, for diffuse involvement of the right upper lobe in two, and for involvement of the whole right lung in one. Of these three, the operation resulted in complete recovery in two and improvement in one. A partial thoracoplasty was done on the remaining 12 cases, with removal of parts of the ribs in the neighborhood of the involved regions. The operation involved the upper six ribs posteriorly in five cases, the lower six ribs posteriorly in one case, and the ninth to the eleventh ribs inclusive in one; with complete recovery in one case, improvement in three, lack of improvement in two and death in two. Of four patients subjected to apicolysis, one completely recovered, two improved and one died. In the remaining case operated

upon, the condition remained the same, in spite of both a posterior and an anterior thoracoplasty of the upper six ribs and apicolysis.

Drainage Operations

Drainage of Empyema Complicating Lung Abscess. The simplest surgical procedure is drainage of empyema when it occurs. Drainage with or without rib resection for empyema secondary to lung abscess may successfully evacuate the lung abscess. Of 13 cases in this group five recovered, one was improved and seven died.

Surgical Drainage of Lung Abscess. Operative interference on the abscess is to be considered after a preliminary trial of rest and postural treatment. Lesions near the chest wall are relatively favorable for surgical drainage. The results are most satisfactory when the abscess is single, but multiple circumscribed lesions may be successfully drained. Diffuse lesions with multiple cavities are in general not suitable for surgical drainage. In recent years the cautery has been used to unroof the abscess cavity. Continuance of foul sputum after operation indicates an undrained pocket. Of 56 cases subjected to open drainage, 16 (28.6 per cent) recovered, 16 (28.6 per cent) were improved, 2 (3.6 per cent) were the same after operation and 22 (39.5 per cent) died.

Cautery Lobectomy. In addition to the opening of the abscess, a more extensive operation may be necessary for the removal of necrotic parts of the affected lung. Of eight such cases, two recovered, three were improved and three died. A complete lobectomy was attempted in two patients, in one by means of the cautery and in the other by exteriorization, and both died.

Summary

The importance in etiology of operations about the upper respiratory tract has increased from one out of every three cases (1909–1924) to one out of every two (1924–1932). Though bronchoscopy is helpful in certain cases in accurately localizing the abscess, it has not proved of value in treatment in the absence of foreign body as a cause. Lipiodol is seldom necessary for the localization of lung abscess, but is of great value in the differentiation of lung abscess from bronchiectasis. The expectation of complete recovery from lung abscess under conservative treatment has risen from about one in every 10 cases (1909–1924) to about one in every five (1924–1932). A short previous duration is one of the most important factors in favorably modifying the chance of spontaneous recovery, which may be estimated at about one in every three cases with a duration of two months or less. A small proportion of patients recover under conservative management after the disturbance has lasted from two to 18 months. Mild and inextensive processes situated at or above the lung root are relatively favorable for recovery without interference.

Of therapeutic measures in our experience evidence is lacking that neoarsphenamine favorably modifies the course of the disease. Regarding collapse therapy, artificial pneumothorax has proved disappointing and entails the serious risk of inducing empyema. Thoracoplasty may be used in carefully selected cases and is at times successful. Suppurative pulmonary lesions differ from tuberculosis with respect to the application of collapse therapy in that drainage is an essential factor in promoting healing. Drainage of a complicating empyema may successfully evacuate a pulmonary abscess. Open drainage of lung abscess is indicated in suitable cases after a trial of rest and postural treatment. Partial cautery lobectomy may be necessary for the removal of necrotic parts of the affected lung.

REFERENCES

1. Lord, F. T.: Contributions to Medical and Biological Research, dedicated to Sir William Osler, 1919, i, 640.
2. Lord, F. T.: Pulmonary abscess, Boston Med. and Surg. Jr., 1925, cxcii, 785–788.

THE NATURE OF PELLAGRA: A CRITIQUE*

By JAMES S. MCLESTER, F.A.C.P., *Birmingham, Alabama*

IN THE first few years of the present century there suddenly appeared in the Alabama Insane Hospital a new disease of unknown nature, the salient characteristics of which were a violent dermatitis of the exposed parts, sore mouth, profuse diarrhea, grave nervous disturbances, and high mortality. The disorder was recognized finally by Searcy, a member of the resident staff, as identical with the pellagra described in the European literature. The rapid spread throughout the Southeastern states of this new and highly fatal disease excited general interest, and concerted efforts were made to determine its cause. Notable among these, but almost forgotten now, was the work of the Thompson-McFadden Commission which during a period of two years made an intensive study of the inhabitants of six mill villages near Spartanburg, South Carolina. The resulting report not only discussed the relationship of certain foods to pellagra but gave interesting data suggesting the conclusion that pellagra is essentially a house disease and that all of the cases of that area could be traced to one focus. A few years later came the carefully planned work of Goldberger who, starting with the prevalent belief that the disease is due to dietary faults, studied the food habits of those people among whom pellagra most frequently appeared, particularly the inmates of orphanages, asylums and prisons. He was signally successful in eliminating this disease, by means of an improved dietary, from two orphanages and an insane asylum in which it had previously been endemic; but the achievement upon which his conclusions largely were based was the production in a group of convicts fed upon deficient diets, of a disease which he and his associates regarded as pellagra. Goldberger's final conclusion that pellagra is due to a specific dietary fault, lack of vitamin G, is now generally accepted the country over, except, it should be noted, in those areas in which the disease occurs with greatest frequency. There, opinion is divided. There are, therefore, two views as to the nature of pellagra, the one, that it is a specific avitaminosis, the other, that there are operative in its causation factors other than a single dietary deficiency. To present this last view is the object of this report.

Two considerations render the avitaminosis theory difficult of acceptance: first the apparent impossibility of invariably relating pellagra to faulty diet or of correcting the disorder by dietary means, and second its epidemiologic characters. The relationship of pellagra to faulty diet is not always clear. True, most pellagrins are poor and their food habits are grievously at fault, but this is not universally true. Time and again I have seen pellagra in a person of ample means whose table was abundantly supplied with the proper

* Received for publication June 1, 1934.

foods, who was apparently well nourished, and in whose diet no gross fault could be detected. Other physicians report similar observations.

I have been deeply impressed also by the difficulty frequently encountered of effectually influencing the course of pellagra by dietary means. We not infrequently see cases in which a balanced ration rich in the vitamin B complex with an abundance of yeast exerts no effect on the fatal course of the disease. The most satisfactory experience I have had has been with liver; at times it works wonders, but occasionally it, too, is of little or no influence. If we conclude that nutritive failure is the sole cause of pellagra, then we must assume that structural damage of such a permanent nature is done that in many instances restoration of the missing factor is of no avail. In most deficiency diseases, notably in scurvy, and in the polyneuritis of fowls correction of the dietary fault accomplishes promptly beneficial, sometimes graphic, results. Not so in pellagra; the result of treatment is much less certain. (Figures 1 and 2.)

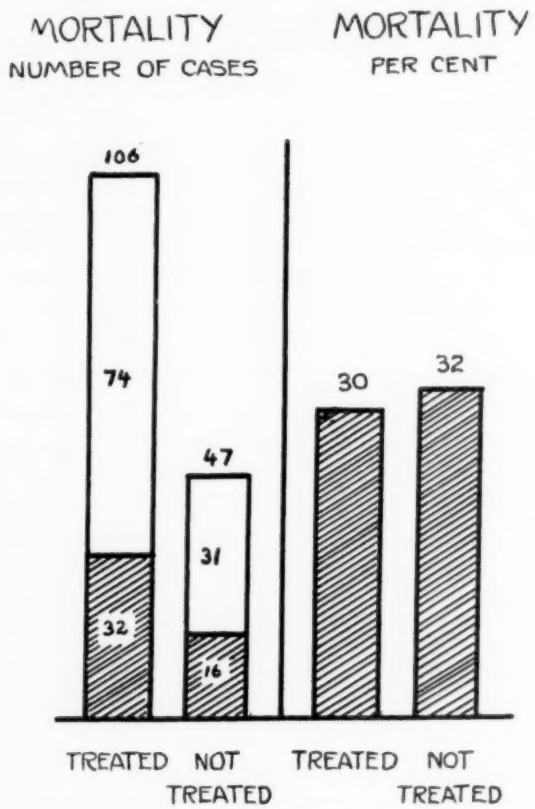


FIG. 1. Pellagra: Hillman Hospital (1920–1933).

The epidemiologic features of pellagra likewise are difficult to reconcile with simple avitaminosis. To those of us who saw this disease when it

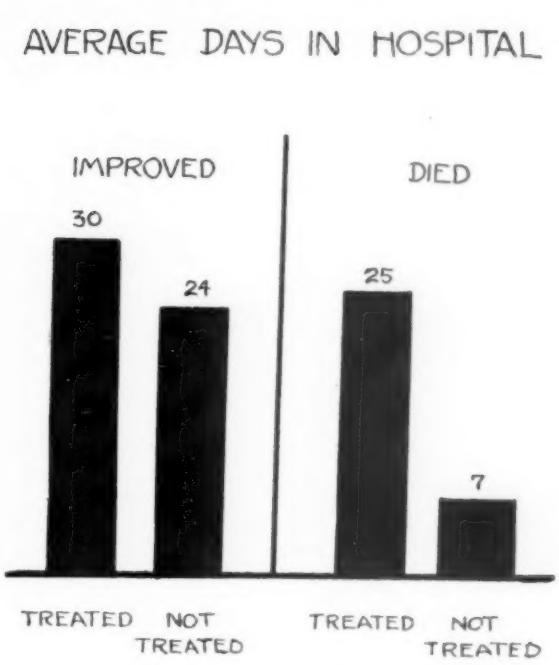


FIG. 2. Pellagra: Hillman Hospital (1920–1933).

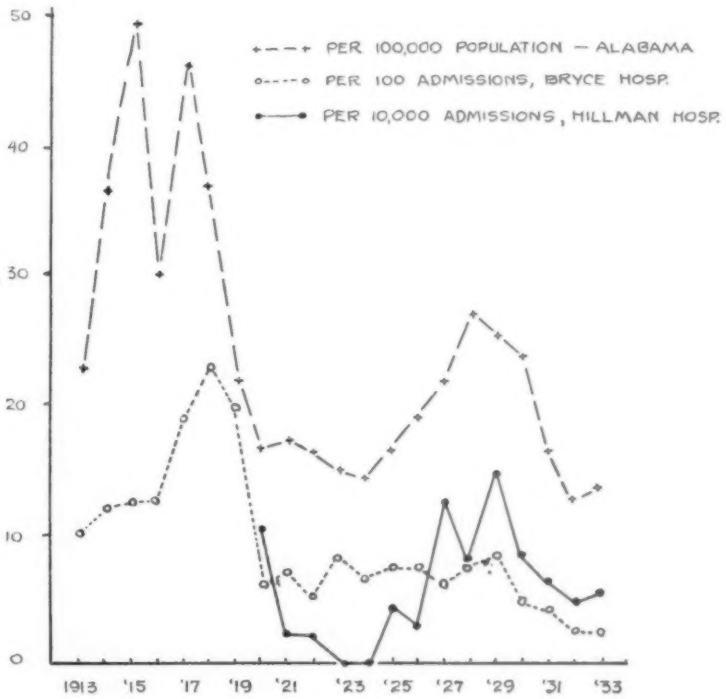


FIG. 3. Pellagra death rates.

first appeared, and who have watched its spread, there come questions that are difficult to answer. Why did pellagra come with such extreme suddenness and spread like a prairie fire throughout the Southeastern states? What is the explanation of the wide fluctuations in the incidence of this disease since its first appearance in America, with, at first, an exceedingly high death rate and then, following successive outbreaks, a steady lowering of the mortality? (Figure 3.) No parallel changes in the food habits of the people have been observed.

Witness the manner in which pellagra, both as individual cases and in epidemic form, seems to spread from definite foci, whether the focus be a single house, a county or a state. (Figure 4.) The data of the Thompson-McFadden Commission indicate that, among people of the same economic status, the hazard of developing pellagra is greatest, vastly so in a house which has harbored a previous case, less in the house next door, and least of all in houses at a distance. Likewise, statistics show that in Alabama the disease has been much more prevalent in neighboring counties (figure 5), and that in the Southeastern part of the country it has been more prevalent in contiguous states. (Figure 6.) Why did this disease exhibit itself in its most violent form among the crowded inmates of orphanages, insane hospitals and prisons? There was no sudden change in the dietary habits of the population, nor were the rations of the affected institutions radically different from what they always were. The Alabama Insane Hospital, for instance, has always maintained large farms and its food supply, which includes milk, vegetables and meat, has remained essentially the same for the past 50 years. Why was pellagra epidemic from 1905 to 1909 in the insane hospitals of Alabama, Georgia and South Carolina, while, during that same period, no case appeared in St. Elizabeth's at Washington or in the insane hospitals of New York state? The food of all of these asylums, North and South, according to the investigations of Partlow, Superintendent of the Alabama Institution, was not essentially different. These features of the epidemiology of pellagra remind one of such communicable diseases as influenza, measles and smallpox rather than of a true deficiency disease.

The experiments of Goldberger and Wheeler were well planned and admirably executed, but examination of their data permits one to question, I feel, the accuracy of their conclusions. Eleven volunteer convicts were given a grossly deficient diet and upon the appearance of certain skin lesions in six of these the diagnosis of pellagra was made. These six men developed a dermatitis upon the scrotum which Dr. Goldberger and the associated dermatologists accepted as evidence of pellagra. Except in two instances, one a dermatitis upon the dorsum of the hands, and the other an erythema of the neck, there was no eruption on the exposed areas. A recognized characteristic of the skin lesion of pellagra is that it comes first, and as a rule solely, upon the exposed parts, notably the forehead, the front of the neck, and the dorsum of the hands, and that these lesions appear most quickly and in most violent form when the patient is exposed to the direct

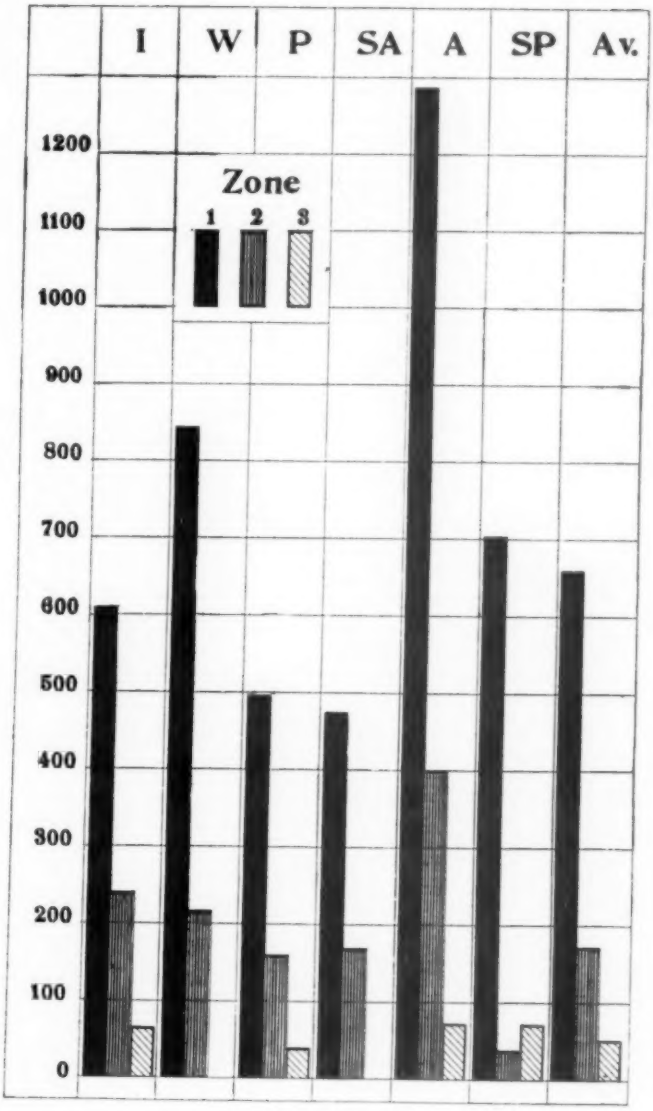


FIG. 4. Location of domicile incident cases per 10,000.

The black columns indicate the incidence of new cases of pellagra among persons living in the same house with a preëxisting case. The columns striped vertically indicate the incidence in the population living next door. The columns striped obliquely indicate the incidence in the population living within the respective village, but farther away than next door from a preëxisting case of pellagra. (Reprinted from Siler, Garrison and McNeal,[1] by permission of the Archives of Internal Medicine.)

rays of the sun. Indeed, the skin of the pellagrin in its sensitivity to the actinic rays of the sun reminds one of the photographic plate, so much so that the suggestion has been made repeatedly that the hypothetical poison

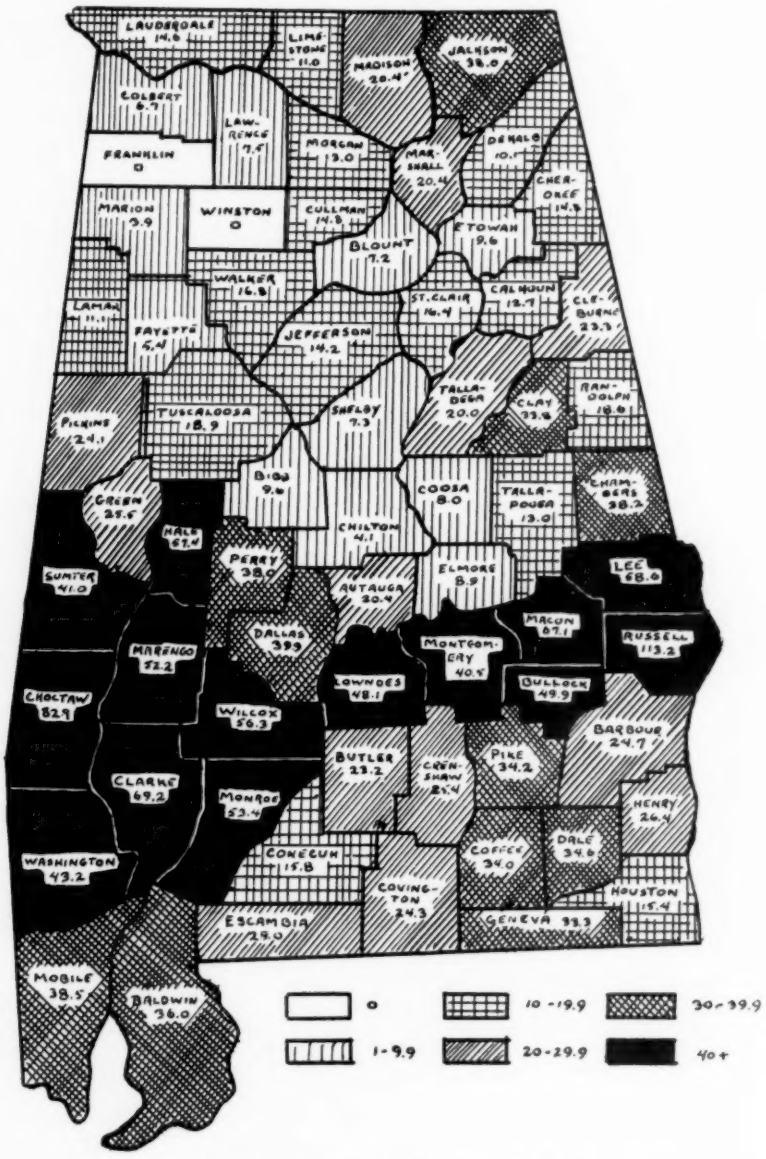


FIG. 5. Pellagra death rate (1929) per 100,000 population.

of this disease has the specific effect of rendering the skin photo-sensitive. I have never seen involvement of the scrotum as the sole or even as the first skin manifestation of pellagra. Of 153 consecutive cases at the Hillman

Hospital in Birmingham, in only one was a genital lesion recorded and this was not the primary skin manifestation. Goldberger told of a few cases exhibiting scrotal lesions quoted from South Africa and of two in America, in addition to certain subsequent observations made by his associate Dr. Wheeler, but he adds, "it remains a fact, however, that the genital lesion whether early or late is a somewhat unusual one." Our experience in Alabama is that it is an extremely unusual one. It is inconceivable to me that these men, working as they were, in the fields of a Mississippi plantation under a midsummer sun should have developed their first lesion on a protected part such as the scrotum, and (except in two instances) shown no lesion whatever upon those parts of the skin exposed to the direct rays of

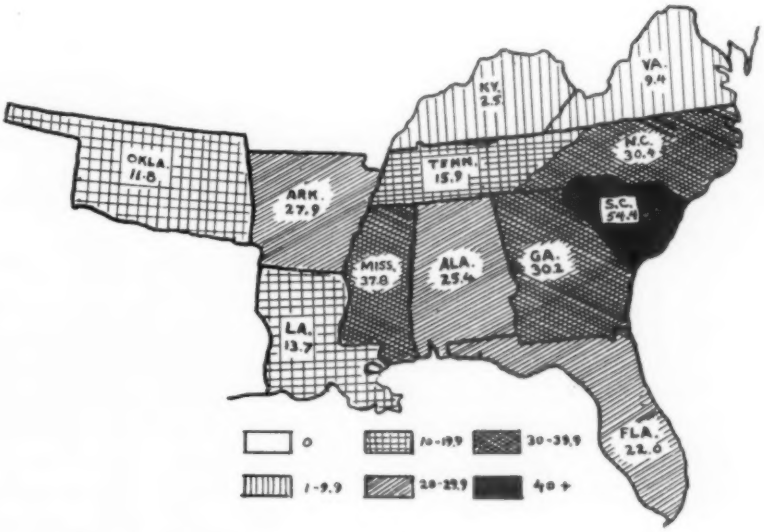


FIG. 6. Pellagra death rate (1929) per 100,000 population.

the sun. The subjects of this experiment, as the report would indicate, experienced the ill effects of a grossly lacking diet, but that they had pellagra is, I believe, open to reasonable doubt.

The work of Goldberger and his associates has been of inestimable value in demonstrating that faulty diet plays a part in the production of pellagra and in pointing the way toward improvement. I am voicing the opinion, of many observant physicians, however, notably those of the hospital in which pellagra has been studied longest, when I express the belief that the true nature of this disease has not yet been fully explained and that a reëxamination of the entire problem would be profitable. Unquestionably nutritional failure plays a part; for most cases, though not all, are associated with faulty diet, and most patients, though not all, get well when properly fed, but the assumption that a single dietary fault is the cause of the disease is far from satisfactory.

What, then, are the possibilities? Two, in the order of their prominence, come immediately to mind. First, that pellagra is the expression of a multiple food deficiency; this could be the result simply of a grossly deficient diet or of some physiologic defect which prevents the proper utilization of food, or indeed, of a combination of the two. Second, that directly or indirectly, an infective agent is concerned in its causation. I do not regard as entirely disproved the belief that pellagra is due to nutritional failure plus the invasion of a specific microörganism. The former conceivably could prepare the way for the latter. The high mortality when the population was first attacked and the gradual lessening in severity, accord with our experience in epidemics of infectious disease; and, since pellagra appears to be a house disease, if we accept tentatively the infectious theory, then there is much which would suggest that this infection is carried by an intermediate host. An infectious nature would explain its sudden appearance and rapid spread, while necessity for a vector would explain its appearance most often among conditions under which personal cleanliness is difficult and in institutions in which over-crowding is the rule.

Such considerations incline me to the belief, notwithstanding the careful work that has gone before, that the last word regarding the nature of pellagra is yet to be said.

REFERENCE

1. Siler, J. F., Garrison, P. E., and McNeal, W. J.: A statistical study of the relation of pellagra to use of certain foods and to location of domicile in six selected industrial communities, Arch. Int. Med., 1924, xiv, 293–373.

THE RECENT TREND TOWARD A DIFFERENTIATION BETWEEN ALLERGY AND IMMUNITY, AND THE RELATIONSHIP TO CLINICAL MEDICINE *

By Lay Martin, M.D., F.A.C.P., *Baltimore, Maryland*

For many years writers have been promulgating the idea that allergy is an integral and essential part of the process of immunity. It has been taught and almost universally believed that the local and general response of allergy has been a necessary, although at times, a dangerous defense reaction in the immunological mechanism. In the past few years a small number of men have questioned this belief and their queries have led to investigations, the results of which point strongly to the idea that allergy and immunity can be dissociated and that the former is not necessary for the proper functioning of the latter.

The object of this paper is to develop the theoretical and investigative facets of the subject and to present to the clinician what is an extremely important, but as yet insufficiently accentuated, problem in medicine.

In medical literature it would be difficult to find more confusion than that which obtains in the interpretation of such terms as allergy, anaphylaxis, hypersensitivity and immunization. At the onset it will be necessary to make clear what meaning and usage will be made of these words in the following exposition.

Allergy is used to represent that delayed reaction which follows the reception into tissues of an antigen to which the tissues are sensitized. It is characterized by edema, inflammation, tissue destruction and necrosis. It is typified by the tuberculin reaction of Koch and the Arthus phenomenon.

Anaphylaxis is used to describe that immediate reaction which takes place in smooth muscle when its sensitized cells come in contact with the antigen to which they are sensitized. It is entirely different in action from the allergic reaction described above and may take place in the water bath by the Schultz-Dale method after all the blood has been removed through perfusion. In the intact animal it is typified by the acute shock of a guinea pig, sensitized to a protein, which has received intravenously a small dose of the specific antigen. The most striking pathologic change is found in the marked distention of the lungs brought about by the spasm of the small bronchiolar musculature; tissue necrosis does not occur.

Hypersensitivity (or hypersensitiveness) is used to express that state of an animal which is allergic or anaphylactic or both. As will be shown below, both states may exist in the same animal and it may be possible temporarily to remove one and leave the other intact. It should only be used as a

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.
From the Gastro-Intestinal Division of the Department of Medicine of The Johns Hopkins Hospital and University.

descriptive term when it is not necessary to designate in more detail the type of sensitization.

Immunization is the word which has done most to cloud the issue. It has been loosely used to describe a number of procedures and of states produced by such procedures. It will be used here to describe the process of making an animal resistant to bacterial invasion or to the effects of bacterial toxin. An immunized animal is one which can withstand bacteria or toxic products which would greatly distress or kill a control animal. It is not used to represent that state which causes an animal to react with dangerous smooth muscular spasm, or inflammation and tissue destruction, to bacteria or a foreign soluble protein, which are non-toxic to normal animals but to which it is sensitized. As the subject is desperately in need of clarification, further discussion, in the hope of simplification, seems permissible.

The early investigators of the effects of diphtheria toxin and toxoid showed that animals could be made immune by injecting the filtrate in gradually increasing amounts. At an early stage substances appeared in the blood stream which neutralized the toxin in measurable amounts. These protective substances were called antitoxins or immune bodies. When toxin was injected into animals properly immunized no reaction occurred and the animals appeared undisturbed.

It was also found that the injection into animals of materials, such as egg white and foreign sera, promoted the production of antibodies which reacted, *in vitro*, with their specific antigens and neutralized them in a way analogous to the toxin-antitoxin combination. The reaction within the animal in this case (when the antigen and antibody united) was not the quiet, harmless union of the diphtheria toxin-antitoxin but an explosive, dramatic affair which more often than not killed the sensitized animal. As antibodies were produced after both the bacterial toxin and the non-toxic protein were injected and as both gave similar test tube reactions, they were both looked upon as immune bodies. That they reacted within the intact animal in different ways was quite evident but both reactions were looked upon as the results of immunization. It was held that the reaction of humoral antibody with the antigen was the method by which the cells were protected against the protein coming in contact with them and causing even greater damage. To call an occurrence such as that which takes place when an innocuous material, egg white, penetrates into the body, an immune reaction is sardonic humor indeed. These animals are not immune: they are hypersensitive. At this time it is of interest to recall a portion of the excellent investigation of Neill, Sugg and Richardson.[1] They have observed that if guinea pigs are repeatedly injected with diphtheria toxin or toxoid they not only develop such antibodies as antitoxin but that after they have been Schick negative for varying periods of time they become hypersensitive. At this time an intravenous injection of the toxoid will produce anaphylactic shock. In animals which have been injected in the usual

manner, no such reaction occurs. It is apparent that these animals were immunized against toxin and later became hypersensitive. To say that they became hypersensitive to the protein of the toxin and not to the toxin itself would seem to beg the question as it is quite probable that these are one and the same thing. These men succeeded in desensitizing some of the hypersensitive animals and their immunity to the toxin remained.

This discussion of anaphylaxis and immunity is perhaps somewhat apart from the main topic, namely the dissociation of allergy and immunity, but it is included as it is quite possible that both forms of hypersensitivity represent responses to a fundamental change in the animal's mechanism.

The difference between the methods of production of the hypersensitive states, anaphylaxis and allergy, is a point of interest. Some investigators find that after intracutaneous injections of bacterial protein or bacteria, they are able to demonstrate allergy but not anaphylaxis; others find that both reactions will occur. Following the intravenous injection of the same materials some investigators find only the anaphylactic response; others see both. The variable in this rather unsatisfactory state of affairs seems to be the dosage and repetition of dosage, of the sensitizing agent. At the present time it appears that when a small dose is given repeatedly, intracutaneously or intravenously, there will be produced respectively an allergic or an anaphylactic type of response. The question is, however, not satisfactorily answered and awaits further investigation. Tables 1 and 2 are included because they indicate the data presented in some of the more recent publications. Study of them will show that there are at least a few points remaining to be clarified.

Robert Koch [2] made the observation that if the tuberculous animal was reinjected with tubercle bacilli a local response developed which was evidenced by edema, inflammation, necrosis and ulcer formation with final healing. The same was true if tuberculin was injected instead of the virulent organisms with the exception that there was rarely ulcer formation. The reaction was a delayed one and reached its culmination in 24 to 48 hours. It came to be known as the *tuberculin reaction* or Koch phenomenon. Von Pirquet [3] became greatly interested and referred to it as allergy (meaning altered tissue reactivity). Subsequently a great many investigations were undertaken and through the excellent demonstrations of Romer,[4] Baldwin,[5] Krause [6] and numerous others, it became widely believed that the tuberculin reaction was to be found only in the presence of a tubercle brought about by infection. Later it was demonstrated by Petroff and Stewart [7] that a sufficient dose of dead tubercle bacilli given parenterally would produce the same result.

It has also been abundantly shown that in those instances in which there was both infection and allergy, the animal was completely resistant to reinfection. Later it was shown that resistance to reinfection and allergy was found after inoculation with heat-killed bacteria and also with an avirulent strain isolated by Trudeau, called R_1.

TABLE I

Immune and Hypersensitive States Induced by Intravenous or Intraperitoneal Inoculation

Investigators	Year	Animal	Sensitising agent	Testing agent	Active sensitization			After desensitization		Passive sensitization		
					Anaphylaxis	Allergy	Immunity	Allergy	Immunity	Anaphylaxis	Allergy	Immunity
Baldwin[36]	1910	Guinea pigs	Tuberculin	Tuberculin	+	0	0	..	..	..	..	..
Baldwin[36]	1910	Guinea pigs	Tubercle B.	Tuberculin	+	+	+	..	..	..	..	..
Austrian[37]	1913	Rabbits and g.p.	Tuberculin	Virulent tubercle B.	+	0	0	..	..	..	..	..
Krause[38]	1916	Guinea pigs	Tuberculin	Virulent tubercle B.	+	0	0	±	0	..	..	..
MacKenzie[18]	1925	Rabbits	Heat-killed pneumococci	Heat-killed pneumococci	+	0	+	..	..	..	..	+
Zinsser and Grinnell[19]	1925	Guinea pigs	Streptococcus	Streptococcus filtrate (a)	..	+	..	..	..	..	..	..
Zinsser and Mueller[39]	1925	Rabbits and g.p.	Defatted tubercle B.	Tuberculin (a)	..	+	..	..	..	..	+	..
Zinsser and Grinnell[40]	1927	Guinea pigs	Pneumococcus autolysate	Pneumococcus autolysate (a)	..	+	..	0	..	..	0	..
Tillett[22]	1928	Rabbits	Heat-killed pneumococcus	Virulent pneumococcus	..	..	+	..	..	..	..	+
Tillett[22]	1928	Rabbits	Nucleoprotein of pneumococcus	Virulent pneumococcus	..	..	0	..	..	..	..	..
Derick and Swift[20]	1929	Rabbits	Non-hemolytic streptococcus	Non-hemolytic streptococcus	+	0	..	..	..	..	..	..
Enders[41]	1929	Guinea pigs	Heat-killed tubercle B.	Tuberculin	+	+	±	+	±	+	0	..
Enders[41]	1929	Guinea pigs	Heat-killed tubercle B.	Carbohydrate fraction	+	0	±	0	±	+	0	..
Bull and McKee[24]	1929	Rabbits	Pneumococcus: heat-killed or nasal infection	Pneumococcus autolysate	+	+	+	..	..	..	..	..
Rich and Brown[25]	1930	Rabbits	Heat-killed pneumococcus	Heat-killed pneumococcus	+	+	+	..	..	..	0	+
Julianelle[21]	1930	Rabbits	Heat-killed pneumococcus	Heat-killed pneumococcus (b)	0	+	+	..	..	..	0	0
Julianelle[21]	1930	Rabbits	Pneumococcus nucleoprotein	Pneumococcus nucleoprotein	0	+	0	..	..	..	+	0
Branch and Cuff[26]	1930	Guinea pigs	Heat-killed tubercle B.	Tuberculin	+	+	+	..	..	..	..	..
Clawson[29]	1932	Rabbits	Heat-killed streptococcus	Virulent streptococcus	+	0	+	..	..	..	..	..
Seibert[30]	1932	Rabbits and g.p.	Purified tuberculin	Purified tuberculin	..	+	..	..	..	..	+	..
Stillman and Goodner[23]	1933	Rabbits	Heat-killed pneumococcus	Heat-killed pneumococcus	..	+	+	..	..	..	..	..

Note:
(a) Intraperitoneal sensitization.
(b) Mice only used to demonstrate passive transfer of immunity.

Krause and numbers of other experienced workers have become convinced that the allergy which accompanies infection is one of the strongest protective weapons at the command of the body. His is the widely known statement, "We believe that specific tubercle immunity occurs through a fixation of germs that result from the operation of the allergic reaction."[6] He believed with Baldwin: "The inflammatory reaction following inoculations of immune animals is the important thing. . . . We are justly entitled to the opinion that cell accumulations about the bacilli are performing the duty of dissolving them or retarding their growth."[5] This theory was strengthened by the investigations of Willis[8] who found that in the normal animal, bacteria left the field of inoculation in a matter of minutes and could be demonstrated in the regional lymph glands in a few hours. In the infected (allergic) animals no organisms were found in the glands until several days had elapsed. This work has recently been corroborated by Freund[9] and

TABLE II

Immune and Hypersensitive States Induced by Intracutaneous Inoculation

Investigators	Year	Animal	Sensitizing agent	Testing agent	Active sensitization			After desensitization		Passive sensitization		
					Anaphylaxis	Allergy	Immunity	Allergy	Immunity	Anaphylaxis	Allergy	Immunity
Koch[2]	1890	Guinea pigs	Tubercle B.	Tuberculin	..	+	+	..	..	..	..	..
Calmette and Guerin[26]	1924	Cattle	BCG	Virulent bovine tubercle B.	..	+	+	0	+	..	..	..
Dochez and Sherman[62]	1925	Rabbits	*Streptococcus scarlatinae* filtrate	Live and killed organisms and filtrate	..	+	..	..	..	..	..	..
MacKenzie[18]	1925	Rabbits	Pneumococcus nucleoprotein	Pneumococcus nucleoprotein	0	+	0	..	..	..	..	..
Zinsser and Mueller[30]	1925	Guinea pigs	Virulent bovine tubercle B.	Tuberculin	..	..	..	..	..	..	+	..
Dochez and Stevens[63]	1927	Rabbits	*Streptococcus erysipelatis* filtrate	*Streptococcus erysipelatis* filtrate	..	+	..	0	..	..	..	..
Bull and McKee[24]	1927	Rabbits	Intranasal infection with pneumococcus	Pneumococcus autolysate	+	+	+	..	..	..	..	..
Goodner[23]	1928	Rabbits	Heat-killed pneumococcus	Virulent pneumococcus	..	+	+	..	..	..	..	..
Derick and Swift[20]	1929	Rabbits	Non-hemolytic streptococcus	Non-hemolytic streptococcus and the nucleoprotein (a)	+	+	+	..	..	..	..	..
Martin and Hill[60]	1929	Guinea pigs	Heat-killed and virulent pneumococci	Heat-killed pneumococci	..	+	..	0	..	..	..	..
Julianelle[21]	1930	Rabbits	Heat-killed pneumococci	Heat-killed pneumococci (b)	..	+	+	..	..	..	0	0
Julianelle[21]	1930	Rabbits	Heat-killed pneumococci	Nucleoprotein of pneumococcus (b)	..	+	0	..	..	..	+	0
Branch and Cuff[28]	1930	Rabbits	Heat-killed tubercle B.	Heat-killed tubercle B. (c)	+	0	+	..	..	..	..	..
Seibert[30]	1932	Rabbits and g.p.	Purified tuberculoprotein	Purified tuberculoprotein	..	+	0	..	..	..	+	..
Clawson[29]	1932	Rabbits	Heat-killed streptococcus	Virulent streptococcus	..	+	0	..	..	..	..	..
Sabin et al.[71]	1933	Rabbits and g.p.	Tuberculoprotein	Virulent tubercle B.	..	+	0	..	..	..	..	..
Friedenwald et al.[34]	1933	Guinea pigs	R_1 tubercle B.	Virulent tubercle B.	..	+	+	0	+	..	..	..
Rich et al.[45]	1933	Rabbits	*Treponema pallidum*	*Treponema pallidum*	..	0	..	..	..	..	..	..
Rich et al.[32]	1933	Rabbits	Heat-killed pneumococci	Heat-killed pneumococci	..	+	+	0	+	..	..	..

Note:
(a) Non-hemolytic streptococcus not a lethal organism.
(b) Mice only used to demonstrate passive transfer of immunity.
(c) Intramuscular inoculations.

complements the observations of Koch who noticed that the regional lymph glands of the reinfected animal did not become enlarged. Along the same line it is important to report the investigations of Opie.[10] He was able to show that none of the egg white, which was injected into the skin of an animal sensitized to it, reached the blood stream; but all was precipitated in the localized Arthus reaction. He believed that the precipitate acted as an irritant and caused the inflammation. This is quite different from the conception of Krause, who believes that the inflammation is a direct result of the union of antigen and sensitized cells.

Coming from such excellent sources the idea gained credence that the allergy found in any bacterial disease is part of the defense reaction of the

body. Among others, Tsuda,[11] Cannon and Pacheco [12] and Menkin [13] have published studies which have added to the weight of this belief. Tsuda states that if specific organisms are injected into sensitized tissue and "if immunity is sufficiently enhanced, the injected cocci at the injected site show the phenomenon of agglutination in the form of follicular clumps and aggregations of microörganisms." He also states that the injected bacteria showed such evidences of degenerative change as swelling, poor staining, and inequality in size. This work was extended by Cannon and Pacheco who found that staphylococci injected into specifically sensitized skin areas tended to agglutinate and clump more readily than in normal animals. They believed that this was helped by the inflammatory reaction and in this they tended to agree with Menkin. He believes that it is due to the inflammatory reactions—specific or non-specific—that a barrier is formed and bacteria are held at the seat of inoculation. From his studies he gained the impression that there is an increased permeability of capillaries in areas of inflammation and that the lymphatics in such fields become obstructed. He demonstrated that foreign particles, when injected intravenously, tend to accumulate in these areas and that if they are injected locally, they are held there. He believes that the increased capillary permeability is the reason for the first finding, and the obstructed lymphatics for the second. His work is excellent but in dealing with the question of antigen in sensitized tissue (allergic reaction) his theories are open to question. A typical allergic reaction does not become fully developed until a few hours after inoculation and it cannot be this delayed reaction which is holding the antigen in check, for in the normal animal, as Willis [8] has shown, the dispersal of bacteria takes place in a matter of minutes. What occurs to hold bacteria there in the immune animal is an important point in the differentiation of allergy and immunity. If it is not allergy, what is it? Before trying to answer this question other conditions must be considered.

As is shown above there is considerable evidence that the allergic response is found in close association with immunity and there is, furthermore, much evidence which might incline one to believe that the reaction is an integral part of immunity. However, in spite of this apparent union there is no proof that in the immune allergic animal the later reaction is essential to the immunological processes; that is, that the edema, inflammation and tissue destruction are essential and that immunity cannot exist in the absence of allergy.

There are a number of observations which cause one to point an accusing finger at the untoward results of allergic reaction and regard it as a dangerous and perhaps unnecessary companion. It is commonly accepted that many of the characteristics of disease entities are based on hypersensitive phenomena. Pleurisy and pericarditis in tuberculosis are commonly accredited to hypersensitivity and there is much evidence that the establishment of this sensitization sets the stage for the development of meningitis and generalized miliary tuberculosis following ulceration of foci in the same

disease. There is evidence that pneumonia develops in animals which have been sensitized to bacteria and soluble proteins (Sharp and Blake,[14] Fried [15]). This has been shown either following intratracheal injection of pneumococcus autolysate into rabbits sensitized with pneumococci or by direct pulmonary injection of horse serum into rabbits specifically sensitized. It is quite possible that tuberculous pneumonia is an allergic reaction. There is much favorable criticism of the idea that the rash of scarlet fever, the joint involvements in rheumatic fever and the glomerular nephritis associated with lymphoid disease, are the result of allergic reaction. It seems quite likely that the intestinal hemorrhages of typhoid fever are brought about by the action of specific antigen on the sensitized lymphatic tissue. In fact, in the whole gamut of diseases it is possible to point out destructive lesions and frequently fatal terminations which are quite probably the result of allergic response. Therefore, it would seem of essential importance to attempt an investigation, planned to demonstrate conclusively whether allergy is an integral part of immunity and if not, whether the animal can recover from infection more easily and promptly in its absence.

Bouquet and Negre [16] in 1928 presented the case for the French investigators in tuberculosis and stated " Immunité et hypersensibilité sont donc deux états distincts et independants des organismes infectés par le bacille de Koch."

Arnold Rich [17] was the first clearly to analyze the situation and he has set a standard of excellence and ingenuity in investigation which will be difficult to surpass. At the onset it should be stated that immunity to various bacteria has been established in a number of species of animal by MacKenzie,[18] Zinsser,[19] Swift,[20] Julianelle,[21] Tillett,[22] Goodner,[23] Bull and McKee,[24] Rich [25] and numerous others. Practically any method which permits sufficient numbers of virulent or heat-killed organisms to penetrate the skin will produce immunity. As noted above, allergy or anaphylaxis or both almost always appear at the same time.

Calmette [26] was much criticized in his immunological attempts with BCG because after a certain period his inoculated children and animals, which had previously been reactive, became refractive to tuberculin skin tests, that is, possessed no demonstrable allergy. He was, however, able to show that in spite of this reprehensible deficiency, as it was called by those of the allergy-being-an-essential-part-of-immunity school, his animals were immune to reinfection. There is still acrimonious discussion concerning the proof of the immunity in children. MacKenzie [18] in 1925 noticed that as he gave rabbits repeated intraperitoneal injections of heat-killed and later virulent pneumococci, his animals became anaphylactic and immune, but even with repeated injections they did not develop antibodies and there was no skin reactivity to the nucleoprotein of pneumococcus. He found that the serum of these rabbits would, when injected intravenously into normal rabbits, protect the latter against many lethal doses of the pneumococcus; this protection was transferred without the accompaniment of allergy. In a

later publication he reported some studies on the effects of repeated skin inoculations of pneumococcus nucleoprotein in rabbits. For about 10 to 14 days the animals became skin reactive but whether they were or were not allergic, their resistance to infection was no different from normals. Julianelle [21] subsequently showed that continued skin activity could be obtained by and to the pneumococcus nucleoprotein but that there was no immunity.

This was indeed an important series of observations for it showed that in the anaphylactic, non-allergic animal there was immunity and further that allergy against pneumococcus proteins was not associated with immunity. Nevertheless, much remained to be done to prove the dissociation of allergy and immunity.

Willis has for years been in agreement with Krause in his belief in the protective nature of allergy. In 1928 he reported [27] that guinea pigs which had been infected two or three years previously with a strain of avirulent human tubercle bacilli (R_1) did not react allergically, as they had done previously, either to tuberculin or virulent H_{37}. They were, however, immune. He made no comment that this was, at least, an indication that allergy was not essential to immunity.

Among the first of the series of experiments noted above, Rich and Brown [25] in 1930 enlarged upon the investigations of MacKenzie. Rabbits were repeatedly injected by vein with large doses of heat-killed organisms; these animals became allergic and immune. It was possible passively to transfer this immunity to rabbits but it was not possible to demonstrate any transfer of allergy. In fact it is very difficult passively to transfer allergy to bacteria although it may be done with bacterial protein products. That same year Branch and Cuff [28] published their observation and among other conclusions stated that "allergy and anaphylaxis in tuberculosis are independent phenomena and immunity may be present without allergy."

In the next few years equally important studies were reported. Clawson [29] compared animals made allergic by repeated intracutaneous injections of heat-killed streptococci with those receiving the same dosage intravenously. The former became allergic, the latter did not. The allergic animals were slower in removing virulent intravenously injected organisms from the blood stream than the non-allergic. Furthermore, at the end of two hours there were more streptococci in the livers of the former group than in those of the latter. He felt that the allergic state did not in any way prevent the spread of disease and that the non-allergic animals had a better chance of recovery.

For a number of years, Florence Seibert [30] has been carrying out a succession of excellently conceived studies on the purification of the tuberculin protein and has finally obtained it in a very pure state. With it she has been able to disprove many of the old tenets on the relation of allergy to immunity, especially in tuberculosis. It was not through lack of trying that allergic responses were not obtained after repeated injections of old tuberculin into animals. It had been tried so often and so diligently that

"no tubercle, no allergy" was a common phrase. By repeated intracutaneous or intravenous injections of tuberculoprotein, in dosages in which the nitrogen content was equal to the amount of egg white nitrogen used in the routine sensitization of animals, she was able to establish in her animals a high grade of allergy which could be passively transferred. In addition to this she found that the allergic animals were not more resistant to inoculation with virulent tubercle bacilli than normals. Sabin and her coworkers [31] corroborated this within a short time; more demonstrations that the allergic response per se is not a valuable protective mechanism.

As it was essential to show that animals which had been both immune and allergic would remain immune after the ability to respond allergically was removed, Rich and Jennings [32] carried out a very ingenuous and clear cut experiment. It is important to recall that those who insist that allergy is an integral portion of immunity, say that it is through the edema, inflammation and tissue destruction produced at the point of entrance of virulent organisms that the bacilli are halted and immobilized until they can be destroyed or ejected. Consequently, if it can be shown in an immune animal, in the absence of edema, inflammation and tissue destruction, that the injected virulent organisms remained grouped at the point of entrance, one's belief in the necessity and benefit of allergic reactions would be at least shaken. Rich and Jennings were able to do this. Rabbits were made highly allergic and immune by repeated intracutaneous injections of heat-killed pneumococci. One-half of the animals were desensitized by the intravenous injection of a large dose of the same vaccine; they were thus rendered immune and non-allergic. These two groups as well as a group of controls received intradermally a virulent suspension of the same bacteria. That which was expected took place: the normal animals (controls) reacted with a typical inflammation which spread over a large skin area; the immune-allergic animals reacted with greater intensity than the controls and the lesions broke down with ulcer formation; the immune-non-allergic animals showed little if any reaction and recovered from the infection fully as well as the immune-allergic ones.

It is in the microscopic sections in this series of animals that a great deal of interest centers.[33] In the controls there was a rapid spread of individual bacteria throughout the tissues. On the other hand in both the immune-allergic and immune-non-allergic groups, the organisms tended to remain in clumps as though agglutinated. Although the clumps slowly enlarged in diameter, there was no distribution of individual organisms through the tissues. One is led to believe that the action of immune antibodies and not the altered tissue reaction (allergy) is the phenomenon which prevents the spread of organisms through the body.

The investigations of Rothschild, Friedenwald, and Bernstein [34] add weight to the observation given above and have a more direct application to the human. They infected a large group of guinea pigs with an R_1 strain of tubercle bacilli, an organism which has been satisfactorily shown

to confer immunity. When allergy was well established these investigators began to inject the test animals with minute but steadily increasing doses of tuberculin. After a period it was possible to give them, without reaction, 1.0 mg. of tuberculin, a dose of sufficient magnitude to kill the untreated infected animals. This dose the normal controls tolerated without demonstrable damage. At this time the three groups were infected intradermally with a virulent human tubercle bacillus, H_{37}. The results were quite conclusive. The local lesion in the untreated control appeared after some days as a small nodule. In the untreated, but R_1 infected animal, a typical tuberculin reaction appeared, reached its full size in 48 hours, and healed after ulcer formation. In the desensitized animals there appeared but a small nodule, no greater than that in the controls, but no evidence of specific tissue reactivity. The control animals became riddled with tubercles; both the desensitized and the untreated R_1 infected animals possessed good immunity. As the desensitizing injections were continued during the six weeks the animals were observed, there is strong evidence that continued lack of allergic response in no degree hindered the immunological process of the animals. In fact, the desensitized animals suffered less for they did not sacrifice tissue through a sloughing ulcer as did the allergic ones.

It has been mentioned above that the proponents of the belief that allergy is of essential importance state that the main protective service of the inflammatory reaction is to restrict the movement of bacteria and to prevent their dissemination. Numerous investigators [44, 45, 46, 47] have shown that although edema is the first change seen in the reacting allergic area, this is soon followed by an influx of polymorphonuclear leukocytes and later by monocytes. It is their idea that the outpouring of leukocytes is important in forming a barrier to prevent the migration of the foreign material. This subject has been clarified by Rich and McKee [35] as follows: After animals were made immune and allergic, sufficient benzol was given them to remove most of their circulating leukocytes; then virulent pneumococci were injected intradermally into these animals and into a group of normal controls. In the control animals the typical inflammatory reaction took place and the invading organisms were surrounded by leukocytes; in the test animals, there was no outpouring of leukocytes or fibrin but the bacteria became closely grouped and remained so. Later the animals died as the immune antibodies could not dispose of the invaders without the aid of leukocytes.

Summary and Conclusions

At this time the investigations bearing on the dissociation of allergy and immunity have abundantly demonstrated certain conditions:

1. Animals which were once allergic and immune have with the passing of time become non-allergic but have remained immune.

2. It has been possible actively to immunize an animal without the concomitant production of allergy.

3. There is ample proof that although animals have become skin reactive to the bacterial proteins, they have not developed immunity.

4. Animals which were allergic and immune have been desensitized without the loss of their immunity.

5. It has been possible passively to transfer immunity to animals without making them allergic.

6. By almost complete removal of the leukocytes from the blood stream of immune animals, it has been possible to show that these cells are not necessary to hold the specific antigen at the point of entrance.

On this basis, one is justified in making the assertion that allergy and immunity are separate reactions and that the former is not necessary for the action of the latter. Because so little work has been done on man, one is not yet justified in categorically stating that it is always wise to remove allergy once it has been acquired; however, the results of the work on animals surely incline one to believe that this may be a good procedure. Equally important to consider is the possibility of actively immunizing individuals without making them hypersensitive.

There is, therefore, opened up a very sensible field for investigation which presents to the clinician the idea that he must seriously consider the establishment of some method of desensitizing the body without decreasing its immunity; tuberculin treatment in the human is an example of this. If the body can be prevented from reacting in an allergic manner, that is, with edema, inflammation and tissue destruction, the infected individual will be spared much discomfort in the course of his disease, and his convalescence may take place more quickly. It may well be that by this means a definite decrease in the mortality from infections will take place; a decrease in that mortality due to the allergic reaction which for years has been considered, without real basis, as an integral portion of immunity.

BIBLIOGRAPHY

1. Neill, J. M., Sugg, J. Y., and Richardson, L. V.: Hypersensitiveness to diphtheria bacterial products; anaphylactic reactions of antitoxic immune guinea pigs, Jr. Immunol., 1930, xix, 109–143.
2. Koch, R.: Fortsetzung der Mittheilungen über ein Heilmittel gegen Tuberculose, Deutsch. med. Wchnschr., 1891, xvii, 101.
3. von Pirquet, C.: Allergie des Lebensalters. Die bösartigen Geschwülste, 1930, G. Thieme, Leipzig.
4. Romer, P. H.: Experimentell-Kritische Untersüchung zur Frage der Tuberculose-Immunität, Ztschr. f. Infectionkrankh. de Haustiere, 1909, vi, 393.
5. Baldwin, O. H.: Immunity in tuberculosis with special reference to racial and clinical manifestations, Harvey Lectures, 1914–15, 155.
6. Krause, A. K.: Remarks on conditions necessary to arouse the allergic state and an immunity through fixation of bacteria, Am. Rev. Tuberc., 1925, xi, 343.
7. Petroff, S. A., and Stewart, F. W.: Immunological studies in tuberculosis; allergic reactions obtained in animals sensitized with killed tubercle bacilli, Jr. Immunol., 1925, x, 677–717.

8. WILLIS, H. S.: Tuberculous infection; early dissemination of tubercle bacilli after intracutaneous inoculation of immune guinea pigs of reinfection, Am. Rev. Tuberc., 1925, xi, 439–449.
9. FREUND, J.: Retardation of tuberculous infection in guinea pigs vaccinated with killed tubercle bacilli as shown by cultural method, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 1200–1203.
10. OPIE, E. L.: Fate of antigen (protein) in animal immunized against it, Jr. Exper. Med., 1924, xxxix, 659–675.
11. TSUDA, S.: Experimentalle Untersuchungen über die entzündliche Reaktion der Subcutis in Beziehung zum Individuellen Immunitätszustand, Virchow's Arch. f. path. Anat., 1923, ccxlvii, 123–150.
12. CANNON, P. R., and PACHECO, G. A.: Studies in tissue-immunity; cellular reactions of skin of guinea pig as influenced by local active immunization, Am. Jr. Path., 1930, vi, 749–766.
13. MENKIN, V.: Studies on inflammation; a factor in mechanism of invasiveness by pyogenic bacteria, Jr. Exper. Med., 1933, lvii, 977–991. (This paper refers to many preceding papers.)
14. SHARP, E. A., and BLAKE, F. G.: Host factors in pathogenesis of pneumococcus pneumonia; reaction of lungs to pneumococcus autolysate in sensitized rabbits, Jr. Exper. Med., 1930, lii, 501–517.
15. FRIED, B. M.: Allergic lobar pneumonia; experimental study, Jr. Exper. Med., 1933, lvii, 111–119.
16. BOUQUET, A., and NEGRE, L.: Sur l'hypersensibilité aux tuberculines et aux bacilles des Koch dans la tuberculose experimentale, Ann. de l'inst. Pasteur, 1926, xl, 11–42.
17. RICH, A. R., and MCCORDOCK, H. A.: Enquiry concerning the rôle of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, xliv, 273–422.
RICH, A. R.: Experimental pathological studies on nature and rôle of bacterial allergy Lancet, 1933, ii, 521–525.
18. MACKENZIE, G. M.: Significance of anaphylaxis in pneumococcus immunity, Jr. Exper. Med., 1925, xli, 53–64.
MACKENZIE, G. M., and WOO, S. T.: The production and significance of cutaneous allergy to pneumococcus protein, Jr. Exper. Med., 1925, xli, 65.
19. ZINSSER, H., and GRINNELL, F. B.: Further studies on bacterial allergy; allergic reactions to hemolytic streptococcus, Jr. Immunol., 1925, x, 725–730.
20. DERICK, C. L., and SWIFT, H. F.: Reactions of rabbits to non-hemolytic streptococci. General tuberculin-like hypersensitiveness, allergy or hyperergy following the secondary reaction, Jr. Exper. Med., 1929, xlix, 615–636.
SWIFT, H. F., and DERICK, C. L.: Reactions of rabbits to non-hemolytic streptococcus; skin reactions in intravenously immunized animals, *ibid.*, 883–897.
21. JULIANELLE, L. A.: Reaction of rabbits to intracutaneous injections of pneumococci and their products. I. Antibody response, Jr. Exper. Med., 1930, li, 441–448. II. Resistance to infection, *ibid.*, 449–462. III. Reactions at site of injection, *ibid.*, 463–472. IV. The development of skin reactivity to derivatives of pneumococcus, *ibid.*, 625–632. V. Development of eye reactivity to derivatives of pneumococci, *ibid.*, 633–642. VI. Hypersensitiveness to pneumococci and their products, *ibid.*, 643–657.
22. TILLETT, W. S.: Active and passive immunity to pneumococcus infection induced in rabbits by immunization with R pneumococci, Jr. Exper. Med., 1928, xlviii, 791–804.
23. GOODNER, K.: Experimental intradermal pneumococcus infection in rabbits, Jr. Exper. Med., 1928, xlviii, 1–20.
STILLMAN, E. G., and GOODNER, K.: Resistance to pneumococcus infection in rabbits following immunizing injections of heat killed pneumococcus suspensions, *ibid.*, 1933, lviii, 195–209.

24. Bull, C. G., and McKee, C. M.: Respiratory immunity in rabbits; intranasal infection and immunization with pneumococci, Am. Jr. Hyg., 1927, vii, 627–634. VII. Resistance to intranasal infection in absence of demonstrable antibodies, *ibid.*, 1929, ix, 490–499. VIII. Rabbits immunized with pneumococcus Types II, III and IV resist intranasal infection with Type I, *ibid.*, x, 229–235. Sensitization of rabbits to products of the pneumococcus resulting from acute infection with this organism, *ibid.*, ix, 666–681.

25. Rich, A. R., and Brown, J. H.: Dissociation of allergy from immunity in pneumococcus infection, Proc. Soc. Exper. Biol. and Med., 1930, xxvii, 695.

26. Calmette, A., and Guerin, C.: Contribution a l'étude de la vaccination de bovidés contre la tuberculose par les voies digestives, Ann. de l'inst. Pasteur, 1907, xxi, 525–532; *ibid.*, 1908, xxii, 689–703. Vaccination des bovidés contra la tuberculose et méthode nouvelle de prophylaxie de la tuberculose bovine, *ibid.*, 1924, xxxviii, 371–398.

Calmette, A.: La prémunition ou vaccination préventive de nouveau-nés contre la tuberculose par le BCG, *ibid.*, 1928, xlii, 1–34.

27. Willis, H. S.: Studies of immunity to tuberculosis; waning of cutaneous hypersensitiveness to tuberculin and relation of tuberculoimmunity to tuberculoallergy, Am. Rev. Tuberc., 1928, xvii, 240–252.

28. Branch, A., and Cuff, J. R.: Tuberculosis. I. Allergic, anaphylactic and immune reactions in guinea pigs following inoculation with heat killed tubercle bacilli, Jr. Infect. Dis., 1930, xlvii, 151–170.

29. Clawson, B. J.: Relation of allergy to general resistance in streptococcic infection, Jr. Infect. Dis., 1933, liii, 157–164.

30. Seibert, F. B.: Chemical composition of active principle of tuberculin; local cutaneous sensitization (Arthus' phenomenon) produced in normal rabbits and guinea pigs by protein of tuberculin, Jr. Exper. Dis., 1932, li, 383–406. Effect of sensitization with tuberculin protein upon development and course of experimental tuberculosis, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 1274–1276.

31. Sabin, F. R., Smithburn, K. C., and Geiger, J. T.: Effects of tuberculo-protein, Trans. Nat. Tuberc. Assoc., 1933, 177.

32. Rich, A. R., Jennings, F. B., and Downing, L. M.: Persistence of immunity after the abolition of allergy by desensitization, Bull. Johns Hopkins Hosp., 1933, liii, 172–196.

33. Rich, A. R.: Mechanism responsible for the prevention of spread of bacteria in the immune body, Bull. Johns Hopkins Hosp., 1933, lii, 203–224.

34. Rothschild, H., Friedenwald, J. S., and Bernstein, C.: The relation of allergy to immunity in tuberculosis, Bull. Johns Hopkins Hosp., 1934, liv, 232.

35. Rich, A. R., and McKee, C. M.: The protective action of antibody in immunized antibodies deprived of leukocytes, Arch. Path., 1932, xiv, 284. A study of the character and degree of protection afforded by the immune state independently of the leukocytes, Bull. Johns Hopkins Hosp., 1934, liv, 277.

36. Baldwin, E. R.: Studies in immunity to tuberculosis, Jr. Med. Res., 1910, xxii, 189–256.

37. Austrian, C. R.: The effect of hypersensitiveness to a tuberculo-protein upon subsequent infection with *Bacillus tuberculosis*, Bull. Johns Hopkins Hosp., 1913, xxiv, 11–25.

38. Krause, A. K.: Studies in immunity to tuberculosis, anaphylactic state in its relationship to resistance to tuberculous infection and tuberculous disease, Jr. Med. Res., 1916, xxxv, 25.

39. Zinsser, H., and Mueller, J. H.: Nature of bacterial allergies, Jr. Exper. Med., 1925, xli, 159–177.

40. Zinsser, H., and Grinnell, F. H.: Further studies on bacterial allergy; antigen involved in pneumococcus allergy, Jr. Bact., 1927, xiv, 301–315.

41. Enders, J. F.: Anaphylactic shock with partial antigen of the tubercle bacillus, Jr. Exper. Med., 1929, l, 777–786.

42. Dochez, A. R., and Sherman, L.: Some reactions in sensitized guinea pigs to the filtrate of scarlatinal streptococcus, Proc. Soc. Exper. Biol. and Med., 1925, xxii, 282.

43. Dochez, A. R., and Stevens, F. A.: Studies on biology of streptococcus; allergic reactions with strains from erysipelas, Jr. Exper. Med., 1927, xlvi, 487–495.
44. Dienes, L., and Mallory, T. B.: Histological studies of hypersensitive reactions; contrast between histological responses in tuberculin (allergic) type and anaphylactic type of skin reactions, Am. Jr. Path., 1932, viii, 689–700.
45. Böhmig, R., and Swift, H. F.: Comparative reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously, Arch. Path., 1933, lv, 611–630.
46. Nye, R. N., and Parker, F., Jr.: Tissue reactions in rabbits following intravenous injection of bacteria, Am. Jr. Path., 1930, vi, 381–400.
47. Hitchcock, C. H., Camero, A. R., and Swift, H. F.: Perivascular reactions in lung and liver following intravenous injection of streptococci into previously sensitized animals, Jr. Exper. Med., 1934, lix, 283–295.
48. Rich, A. R., Chesney, A. M., and Turner, T. B.: Experiments demonstrating that acquired immunity in syphilis is not dependent upon allergic inflammation, Bull. Johns Hopkins Hosp., 1933, lii, 179–202.
49. Martin, L., and Hill, J. H.: Development of skin sensitization in guinea-pigs in response to intradermal injections of bacteria, Bull. Johns Hopkins Hosp., 1930, xlvi, 246–253. Milk protein as inhibitor of skin sensitization in guinea-pigs previously injected intradermally with pneumococci, *ibid.*, 254–258.

EARLY RECOGNITION OF MYOCARDIAL DISEASE*

By WALTER L. BIERRING, M.D., F.A.C.P., *Des Moines, Iowa*

THE diagnostic signs of myocardial disease may be grouped under two classes: first those which are based on morphologic changes with obvious physical symptoms that make a direct appeal to the senses, and second those that are based on functional reactions, entirely subjective in character and often not susceptible to recognition by the human sense organs.

In general practice two or possibly three distinct types of heart disease are encountered. In childhood and young life the valvular affections prevail, usually the sequel of the acute infectious diseases, principally rheumatic and streptococcic infections which generally attack the valvular endocardium, but may involve the pericardium and myocardium. Diphtheria, typhoid and the influenzal group of infections are further etiologic factors. The resulting heart disease is recognized mainly by physical signs, subjective phenomena having a minor place in diagnosis.

With middle life the effects of syphilis on the cardio-vascular system become more manifest. Widening of the aorta area and accentuation of the second aortic tone are significant of the aortitis so common to this form of heart disease.

The third type belongs to the aging period in the middle and later decades of life, often noted in the prime of life. This form of heart disease is quite a different process, being largely the result of wear and tear with nutritive disturbances affecting principally the cardiac musculature and leading to degenerative changes with replacement fibrosis. Its etiology is indefinite and often as obscure as the associated conditions of arteriosclerosis and hypertension. Clinically it has no manifest or clear cut physical signs until the later or terminal stages of the process. The subjective story is often very suggestive and diagnostic of the condition. Distinctive and characteristic clinical pictures have been developed for the several advanced or terminal stages. Acute coronary thrombosis is now recognized as a distinct clinical entity, and its prompt diagnosis is of common occurrence. Chronic coronary artery disease or coronary sclerosis, likewise permits of ready diagnosis.

The clinical evaluation of heart disease of all forms centers more and more around the question of the integrity of the myocardium. Myocardial failure or insufficiency of varying degrees is associated with valvular disease and the different forms of chronic heart disease. Its symptomatology is familiar and requires no repetition.

The clinical onset in the chronic types is often of striking suddenness, occurring in individuals previously in apparently good health, yet in each

* Read at the Chicago meeting of the American College of Physicians, April 19, 1934.

condition it is safe to assume the existence of basic anatomic changes in the myocardium that have required a long period, probably years, to develop.

It is in this developmental period that the clinical syndrome of the early stage of myocardial impairment may be detected. Patients passing through this stage comprise rather a large group; they come to the attention particularly of the general practitioner and the dispensary or out-patient clinic, and are seen less frequently in a consulting practice.

It seems unfortunate in some respects that heart diseases have become a highly specialized field of medicine, and to a large extent have been taken out of general practice. Mackenzie [1] always contended that the general practitioner, by reason of his familiarity with the habits and history of the patient, was able to detect the earliest signs of disease.

The phenomena included in this syndrome or grouping of symptoms in early myocardial disease are almost entirely subjective, and perhaps have no definite sequence, yet considered concurrently they present a rather suggestive symptom complex. In a large measure these phenomena are expressive of a lowered myocardial reserve, and as such they have been considered by other observers.

The need of a careful history is evident, and its completeness will depend on the art and ability of the examiner to draw out of the patient the essential subjective complaints. The history should include a careful investigation of previous infections, particularly such as could produce damage of the myocardium; next, information as to the presence of a familial tendency toward diseases of the circulation is important; and, lastly, a definite history as to the various indiscretions of life which tend toward early vascular changes.

The leading symptom of this syndrome is fatiguability. Clinicians are in accord that cardiac fatigue is one of the early signs of myocardial weakness. It represents a patient's reaction to effort, and is generally expressed as tiring or fatigue after the ordinary efforts or habits of his vocation and daily order of life.

The complaint is often of a tired feeling in the legs, more noticeable toward the end of the day. Frequently it is stated that he " is not as good as he used to be." Often there is added the element of fear, or disinclination to perform the usual tasks.

Fatigue is a sensation known to everyone and the term is often loosely applied. It may not be realized that its signs and symptoms affect every body tissue—glands, sense organs, and central nervous system, being just as susceptible as the muscles.

As Wiggers,[2] the physiologist, has aptly stated, functional reactions in disease differ from those in health only in degree, and there are no pathologic processes in disease capable of evolving new types of functional reactions. The physiologic conception is that manifestations of fatigue are direct criteria of an oxygen debt and of the accumulation of lactic acid. The more rapid development of fatigue in heart disease merely signifies a

deficiency on the part of the cardio-respiratory system in meeting the increased demands of muscles during exercise.

Expressed in another way, the physiologic ability to respond to exercise without fatigue becomes a direct measure of the compensatory mechanism held in reserve by the heart; that is, the myocardial reserve.

The inability of the diseased heart to compensate for this circulatory inefficiency is due to loss of the myocardial reserve. Again it may be said that in heart disease the oxygen debt is incurred with a less amount of work, and lactic acid accumulates more rapidly.

It may be assumed that with early changes in the coronary circulation the inefficiency of the heart muscle will be manifested by cardiac fatigue.

Circulatory fatigue may show itself in the form of insomnia, which can be grouped among the early signs of lowered myocardial reserve.

The mimicry of gastric symptoms in advanced coronary disease is well known, and it is logical that to a lesser degree this occurs in connection with myocardial weakness. These are expressed under the guise of loss of appetite, gaseous distention and a feeling of pressure in the upper part of the abdomen, the chemical and roentgenologic manifestations being negative. Riesman [3] has aptly referred to them as gastric masquerades, adding that apparent disease in the upper abdomen often has its seat of origin in the heart.

Certain vasomotor disturbances are a definite part of this syndrome, such as vertigo, giddiness, syncope and occasionally convulsions. Again such psychic phenomena are noted as mental haziness, impaired memory, stupor, drowsiness and hallucinations of sight, hearing and smell. It seems well determined that aside from primary disorders of the nervous system or chemical alterations of the blood, cardio-vascular disorders are frequently responsible for the symptoms of dizziness, unconsciousness, and the psychic phenomena previously referred to. The cells of the cerebral cortex are extremely sensitive to any marked diminution of its supply of oxygenated blood even though temporary, and react promptly by the manifestations as stated. These occur often with simple postural changes, as lacing a shoe, bending forward suddenly, or other movements incident to the occupation of the individual.

Recent investigations have shown that the metabolism of the brain does not differ greatly from that of other tissues. The rate of lactic acid formation in the brain tissue appears to be higher than that of the body as a whole, and the normal blood flow per gram of brain substance is larger than that for skeletal muscle, heart, liver or spleen. It is not surprising, therefore, that cerebral activity should be seriously affected in conditions of reduced myocardial reserve as well as in advanced stages of decompensation. These somewhat vague phenomena may accompany or usher in that triad of symptoms which Kauffman [4] has termed the three steps to heart failure: (a) breathlessness, (b) palpitation, and (c) substernal discomfort.

Breathlessness is probably the most important feature of this syndrome, but it again requires a fine distinction to determine whether this is a normal physiologic response or a pathologic manifestation. It is important to determine whether the change in functional response to certain effort tests such as climbing stairs, walking up a slight incline, and daily routine duties are phenomena that have not been noticed before. Often the time taken to return to the resting state will be longer and sometimes painful.

Long before the stage of circulatory failure is reached, the patient with heart disease differs apparently from normal persons only in the degree of muscular activity that brings on dyspnea and weakness.

The normal individual is ordinarily not conscious of the vigorous normal movements of the heart, because he has become accustomed to them. The sign of *heart consciousness,* as manifested by flutter, skipping beats, thumping and palpitations, occurring in middle life after a meal or physical effort, should therefore be given careful evaluation. It is specially significant if such symptoms have not been noted previously. When associated with breathlessness and fatigue, heart consciousness becomes an important part of the total syndrome.

The sensation of *substernal discomfort* is the one symptom that most frequently causes the patient to seek medical advice. Like the expression "heart consciousness," it is a sensation that is difficult for the average patient to describe. Some express it better than others. The sensations apparently may extend from a mere feeling of heaviness over the upper part of the chest to the terrible vice-like constriction experienced in certain forms of angina pectoris. Herrick [5] has referred to the lesser forms of substernal discomfort as a mild type of angina. That it is invariably associated with physical effort still further confirms this relationship.

Substernal discomfort or distress, unlike breathlessness and palpitation, is rarely masked under any other guise. It is localized more frequently to the left than to the right of the upper part of the chest and radiation is uncommon.

While the subjective phenomena constitute the essential part of this syndrome, certain physical or objective signs have an important relation to it. Of these a demonstrable enlargement of the heart has assumed a primal importance in the recognition of early myocardial disease. Christian,[6] Stroud,[7] Eyster [8] and others have given special significance to this symptom. Eyster considers that the differentiation of the enlarged heart from the heart of normal size is the most important single factor in determining the presence or absence of organic heart disease.

The greatly hypertrophied heart in advanced organic disease is easily recognized by the usual methods of physical examination, but there is need for more accurate differentiation of the hearts that are less abnormal and associated with an earlier stage in the pathologic process.

Studies in most of the lower animals have shown that the weight of

the heart is more closely related to the size of the body than is the weight of any other organ with the exception, perhaps, of the brain.

An estimation of the cardiac size in man can be made only indirectly by the projection of one or more of the surface planes of the heart. Of the two general methods employed for this purpose topographic percussion, and the roentgen-ray projection, the latter is now considered more objective and accurate.

In a series of contributions from 1924 to 1928, Hodges [9] and Eyster [10] established tables predicting cardiac area and cardiac transverse diameter in the frontal plane from height, weight and age, as criteria for determining the presence or absence of cardiac enlargement. These were adopted in 1931 by the Heart Committee of the New York Tuberculosis and Health Association and are now recommended by the medical departments of many life insurance companies. These tables are now generally regarded as the most accurate standard available, when used with postero-anterior roentgen-ray plates; and this method is considered superior to the use of the cardio-thoracic ratio.

While the tendency is to a most complete use of the roentgen-ray in examination of the gastrointestinal tract, it receives much less consideration in cardiac disease, although it is of equal importance. By means of the fluoroscope, orthodiascope, teleroentgenogram and signs of either right or left ventricular preponderance in the electrocardiogram, definite evidence is presented of the degree of cardiac enlargement.

The truest estimate of encroachment on myocardial reserve is therefore best arrived at by the determination of cardiac enlargement. The presence of cardiac enlargement is always of potential significance; it may be the earliest physical sign of myocardial impairment. Of minor import are blood pressure changes as the result of physical exertion. These have been variously interpreted. No satisfactory exercise test has yet been devised. An elevation of 20 mm. of mercury after one of the customary exercise tests is regarded as a sign of myocardial weakness. A change in the pulse rate after exertion is also regarded as having some diagnostic significance. When the pulse rate requires longer than five minutes to return to the resting figure, it suggests an impairment of myocardial reserve.

Venous Pressure

Recent observations on venous pressure and its more extensive use in clinical examinations suggest that it has a significant relation to the dynamics of the failing heart. Eyster [11] reaches the conclusion that venous pressure is clinically an index of cardiac function and that its clinical significance is largely confined to the one condition of impending or present cardiac incompetence. Venous pressure in cardiac insufficiency varies from the upper normal level (100–110 mm.) to 300 mm. of water or more. The extent of the failure is roughly proportional to the rise, and the clinical

progress of the patient and the prognosis of the condition are largely revealed by the trend of venous pressure. Frequently a change in venous pressure precedes other clinical signs. Cardiac incompetence has been described as that condition in which the venous pressure exceeds the range within which the heart is capable of responding by increased work to an increased venous load.

Electrocardiography

The electrocardiogram in the early stage of myocardial disease has thus far not been regarded as of especial significance. Signs of conduction disturbance and changes in the ventricular complex are most apt to be found. Left axis deviation occurs so frequently in middle and advanced age periods that many observers regard such a sign as normal; yet, on the other hand, interesting studies have been reported by Luten and Grove,[12] and more recently by Hyman and Parsonnet,[13] that are very suggestive. In observing the development of bundle branch block from the beginning, they noted that the cases showing early left axial deviation with altered T-waves in the first lead later developed into full blown bundle branch block. As more frequent and serial electrocardiographic studies are made, particularly as additional leads will clear up the so-called silent areas, it is reasonable to expect that early changes will be noted that will prove of diagnostic value.

The nosology or description of the diseases of the heart has varied and kept pace with the changing conceptions of the underlying physiologic and pathologic processes.

Various clinical terms have been proposed for the degenerative type of cardiac disease. While chronic myocarditis has been the usual designation, it is not very expressive nor properly related to the existing disease condition.

Christian [14] has proposed the term chronic non-valvular heart disease, yet admitting that it was not entirely satisfactory.

For the syndrome or group of phenomena, subjective and objective, encompassed in the early stages of myocardial impairment, the term myocardosis has been suggested, being first proposed by Riesman [15] in 1926; Hyman and Parsonnet [16] have published several comprehensive articles under this title. It is a generic term signifying myocardial disease and in that sense rather expressive of the condition. Considered separately, each phenomenon occurring in myocardosis is not diagnostic, but taken concurrently they form a clinical picture that permits of ready recognition. The term is mainly expressive of the myocardial reserve of the heart, which is an important factor in the complicated mechanism of the circulation; and it is likewise suggestive of early anatomic changes in the myocardium. The field of early myocardial disease is open for fruitful investigation, and it offers alluring prospects in the study of the various phases and stages of coronary disease now beyond our ken.

The early recognition of myocardial disease entails a considerable responsibility on the attending physician. The public has a greater fear of

heart disease than of any other disease, except cancer or perhaps syphilis. As Herrick [17] has said, it is easy to sow the seed of fear of heart disease. Phobias may be started and neurotic individuals made more neurotic with a consequent lessening of their activities and happiness. Yet the fullest coöperation of the patient is needed if during the early stages any attempt is to be made to curb or combat the relentless progression of the vascular degenerative changes in the heart peculiar to the middle and later decades of life. It is of primal importance that the patient accept the view that the aging process is a physiologic change and does not permit the same activities as in younger years. When the condition clearly indicates an encroachment on the normal myocardial reserve, rest and limitation of activities should be the main essential in outlining a proper regimen of living.

The proper appreciation of the syndrome of early myocardial disease offers the one hope of modifying and possibly controlling the tendency to progressive and more serious myocardial damage; and, above all, it opens up a new field in preventive medicine that is worthy of our best efforts.

REFERENCES

1. Mackenzie, J.: Symptoms and their interpretations, 1918, Paul B. Hoeber, Inc., New York.
2. Wiggers, C. J.: Physiologic meaning of common clinical signs and symptoms in cardiovascular disease, Jr. Am. Med. Assoc., 1931, xcvi, 603–610.
3. Riesman, D.: Myocardial disease and its gastric masquerades, Jr. Am. Med. Assoc., 1928, xci, 1521–1523.
4. Kauffman, R.: Über Probleme des Koronararterien-Kreislaufes, Wien. klin. Wchnschr., 1926, xxxix, 437, 477.
5. Herrick, J. B.: Angina pectoris, Northwest Med., 1925, xxiv, 360–367.
6. Christian, H. A.: Chronic nonvalvular cardiac disease or myocardial insufficiency and its therapeutic management, Ann. Int. Med., 1931, v, 95–99.
7. Stroud, W. D.: Importance and most satisfactory clinical methods of estimating myocardial reserve, Am. Heart Jr., 1926, i, 354–358.
8. Eyster, J. A. E.: Determination of cardiac hypertrophy by roentgen-ray methods, Arch. Int. Med., 1928, xli, 667–682.
9. Hodges, P. C.: Comparison of teleroentgenogram with orthodiagram, Am. Jr. Roent., 1924, xi, 466–474.
10. Hodges, F. J., and Eyster, J. A. E.: Estimation of transverse cardiac diameter in man, Arch. Int. Med., 1926, xxxvii, 707–714.
11. Eyster, J. A. E.: Venous pressure, Jr. Am. Med. Assoc., 1931, xcvii, 1269–1271.
12. Luten, D., and Grove, E.: Incidence and significance of electrocardiograms showing features of left axis deviation and QRS of normal duration with inverted T_1 and upright T_3, Am. Heart Jr., 1929, iv, 431–441.
13. Hyman, A. S., and Parsonnet, A. E.: Bundle branch block; phenomena of its development in relation to axis deviation of heart, Arch. Int. Med., 1930, xlv, 868–878.
14. Christian, H. A.: Chronic nonvalvular disease of heart, Jr. Am. Med. Assoc., 1928, xci, 549–552.
15. Riesman, D.: Diagnosis and treatment of acute and chronic myocardial weakness, Med. Clin. N. Am., 1926, x, 261–271.
16. Hyman, A. S., and Parsonnet, A. E.: Myocardosis, Jr. Am. Med. Assoc., 1930, xciv, 1645–1646. The failing heart of middle life, 1932, F. A. Davis Co., Philadelphia.
17. Herrick, J. B.: Common errors in treatment of heart disease, Jr. Med. Assoc. Ga., 1931, xx, 335–343.

STUDIES OF CELL POTENCIES AND SOME RELATIONS TO NEOPLASIA *

By STANLEY P. REIMANN, *Philadelphia, Pennsylvania*

THERE is a timed sequence of three fundamentals concerned in any increase in cell number in multicellular organisms, and these are the processes of proliferation, differentiation and organization. Since they are dynamic processes which proceed in regular but overlapping order at any given stage of growth and development, it is exceedingly difficult to experiment with them in the higher animals, including man. Both observation and experiment are easier in lower animals, and because they are so fundamental and occur in all types of living things, it is justified to study them in any organisms in which the experimental conditions can be simplified. Especially important is it that their dynamics be studied, that each be segregated from the others, that one or the other be interrupted separately at various points, that the time relations be manipulated, and so on.

To make the terms themselves clear, definitions of them can be given as follows: Proliferation is simply the multiplication of cells. Differentiation is the changes in the cells which lead from the more general to the more specific; or at another stage of the process: differentiation is the result of that series of changes occurring within the protoplasm of cells which bring them to the point of being able to perform their functions as members of an adult organism. Organization may be defined as the harmonious, cooperative development of cells of various differentiations so that they can function in the frame of a whole organism.

Proliferation is a function common to protoplasm in whatever living thing it is found. Differentiation and organization, on the other hand, lead to the development of the anatomic and functional peculiarities of each individual, species, genus and family. They are, in other words, the processes which lead to the production of a human from a human fertilized ovum, a dog from a dog fertilized ovum, and so on. Obviously, the factors which determine differentiation and organization are contained within cells and come from parents. We might stress further the point that of the two, organization is the more specific, for differentiations in similar directions occur in many unlike organisms as, for instance, both giraffes and humans have epithelial cells, whereas strict specificity, that is, the way epithelial cells and others are arranged, is what determines that a human is built upon human plans.

Another obvious point in the relations between the three processes is that when differentiation and especially organization have occurred to the extent of producing an example of the proper species, proliferation ceases.

* Received for publication June 2, 1934.
From the Lankenau Hospital Research Institute, Philadelphia, Pennsylvania.

Therefore differentiation, and especially organization, are natural inhibitors of proliferation. Still another relation is obvious when we put it in this form: cells cannot differentiate and organize unless they are present. Therefore proliferation is a necessary preliminary to the others. An important deduction is, that if differentiation and organization do not occur, cells continue to proliferate, e.g., in tissue cultures. Also when organization is disturbed as by an injury, proliferation begins to repair the injury and continues until organization again puts a stop to it.

Now the relation to neoplasia can be put in some such wise: the cells of all tumors proliferate, else, of course, they would not grow. The cells of many tumors differentiate, sometimes fairly perfectly, but the cells of no tumors organize normally. Since, therefore, the factors governing differentiation and organization are present within the cells and since tumors often grow in the very same environment in which normal cells are differentiating and organizing, it would seem that the cause of tumors lies in a failure of their differentiating and especially their organizing powers, or potencies, to introduce this term. Shall we say, then, that the cause of the continued growth of tumors is the failure of their cells to differentiate, and especially organize, properly?

The experiments to be described were directed toward the proliferative phase of cell growth and development. This is an extension of the use of the new tool—sulfhydryl. The story of F. S. Hammett's discovery of this sulfhydryl group as a normal, essential chemical stimulus to cell division and his demonstration that partially oxidized derivatives of this group inhibit cell division has been told before. Suffice it to say, that up to the present, cell division in some 40 odd species of animals and plants, including man, has been found responsive. Results obtained with this reduced-partially oxidized sulfur equilibrium can be translated directly in terms of the normal, something which could not be done until it was discovered, and cannot be done when extraneous cell-division stimuli are used such as tar, roentgen-rays, scarlet red and many others.

The experimental material which I will now show consists of the skins of rats, mice and guinea pigs, and the regenerating claws of hermit crabs. Both were subjected to sulfhydryl, the one to simple application to their skins, the other to living in sea water to which sulfhydryl was added. In addition the crabs were subjected to partially-oxidized sulfur, the inhibitant.

The skins of rats, mice and guinea pigs are simpler than those of humans and consist of a few layers of epithelial cells with no regular arrangement of basal layers, spinous cell layers, pigmented layers. A few groups of cells in the middle layers show spinous structure, a few pigmented cells are found and a few are oriented vertically in the basal layers. After application of the sulfhydryl group, the picture changes amazingly. The cells in the basal layer are practically all oriented vertically as a result of their increased mitotic activity; a definite basement membrane appears. A full and complete layer of spinous cells appears, and a layer of pigmented cells.

The increased number of epithelial cells comes from the younger, incompletely differentiated cells of the skin. Adult, fully differentiated epithelial cells of the skin are incapable of division.

In all probability, this latter statement can be expanded to the point of declaring that when any cell is completely differentiated it can no longer multiply. Needless to say, this is extraordinarily difficult to prove, if for no other reason than that accurate methods of quantitative measurements of degrees of differentiation of cells are still to be worked out. Among other implications of this statement, however, are these: wherever continuous or interrupted cell multiplication occurs there must be present " spare parts," so to speak, from which the multiplication can begin; and cells in any given organ or part which retain the power of multiplication for whatever reason, physiological increase in number, repair, regeneration, etc., are not fully differentiated. Which, in turn, means that evolution has not ceased. But will anyone say it has?

At any rate this is a specific reason for the previous statement that differentiation and organization are natural inhibitors of proliferation.

To return to the mouse skins, I repeat from Hammett's interpretation of the biological significance of the picture: the stimulation to rapid division results secondarily in an expansion in the rate and degree of the differentiating and organizing potencies of the cells.

If, then, experimental increase in the rate of cell division obtained with a natural stimulus—sulfhydryl—results not in diminished, but in increased differentiation and organization of the cells so stimulated, it follows that increased rate of cell division alone can never lead to malignancy. Something must happen to their differentiating and especially organizing potencies. Incidentally this is why sulfhydryl alone should not produce malignancy.

Suppose the rate of cell division which is normal to any given growth and developmental process be retarded. Hammett has shown with partially-oxidized sulfur groups in a variety of material what happens then. Conversely, when the rate of cell division is retarded, so also are the degrees of differentiation and organization. But at any given time period, comparison of the retarded material with that of the controls shows that the retarded material is identical with the controls of an earlier time. Therefore decreased rate of cell division alone does not lead to malignancy. I use diagrams (published elsewhere) of regenerating hermit crab claws under the influence of sulfhydryl, sulfoxide, and the appropriate controls to illustrate these points.

In 269 regenerating claws which were studied, 44 growth aberrations were found. A study of them by serial section and comparison with the normals allows an answer to another question.

It is obvious that the sequence under discussion, viz., proliferation, differentiation and organization, must be timed properly or an abnormal part will be produced. Will this abnormal part be a neoplasm, or will it,

in the end, organize as best it can, bring proliferation to a stop, and result in merely a growth anomaly? The answer as written in the crab claws is as follows.

In some of the claws, breaks in the chitinous envelope, being laid down as the new claw regenerated, opened this barrier to the proliferating cells. They streamed through and produced an unorganized mass. Since sulfhydryl is a specific stimulus to proliferation, all those claws with defects which were exposed to this chemical group developed growths, and all of them were much larger than those which appeared in the controls (75 per cent), or in the retarded, i.e., sulfoxide-treated, specimens (43 per cent). In other claws unorganized growths were found at the tips of the distal segment of the claw. Study of serial sections and of timed specimens showed that differentiation and organization were progressing in addition to the proliferation, but that the timing of these processes was thrown out of gear. There is no doubt that the growths would eventually have ceased proliferating and smoothed out to a bump on the claws.

Several other specimens of special interest were found, such as a hyperchitinosis corresponding to hyperkeratosis, and a second regenerate attempting to grow within the stump. In all of these the same phenomena occurred, viz., the potencies of differentiation and organization within the cells attempted expression, even though the time relations were disturbed and the environment was changed. Important to the present consideration is the fact that proliferation was inhibited.

Space forbids further discussion, even though but a very few of the fundamentals involved in these experiments have been touched upon; really they have only been mentioned. One of the many practical applications may be hastily sketched, however. The time factor is often the crux of the situation in the ordinary pathological diagnosis of tissue. In the edges of gastric ulcers, epithelium is often found in the midst of granulation tissue and the question arises: Is this repair or carcinoma? What would have happened if the surgeon had not removed the ulcer when he did? If merely the relative rates of proliferation, differentiation and organization have been shifted, it is not carcinoma. Nor is it carcinoma if the cells ensnared in a different environment are attempting to express the normal potencies of differentiation and organization within them. That much discussed, but quite impractical subject of tumor grading also is more than touched by these considerations.

What then is the distinguishing feature of malignancy? Increasing the rate of cell division does not change these potencies, in fact it allows of more full expression. Decreasing the rate does not cause neoplasia. Facts from which we cannot escape are that the cells of neoplasms differentiate imperfectly and do not organize, even when in the very same environment in which normal cells are accomplishing these processes. Nor is it a fault in timing, as even the inexperienced in oncology can testify, and as the experiments discussed above show. Since the potencies of differentiation

and organization are contained within the cells, the fundamental cause of neoplasia must be a change within them.

That there are degrees to this change is also evidenced by numerous facts. The better the differentiation of the cells of a tumor, the slower its growth as tumor grading in its statistical application has shown. But this is but in harmony with the biological truism that the less mature an embryo, the more rapid its growth. In other words, malignancy and benignancy of a neoplasm, in the sense of its rate of proliferation, its invasive properties, its autonomy, etc., can be directly correlated with its deviation from the appearance of the structure which normal cells would produce under the same circumstances.

I, as well as others, have been dissatisfied with even the definition of what a neoplasm is, let alone with many of the views on the subject. In summing up, as good a way as any is to do it in the form of a definition. For the time being, and until and unless more knowledge demands its revision, we say that a neoplasm is a mass of cells which arises from and continues to proliferate within an organism as a result of and in direct proportion to their degree of internal qualitative differences from the other cells of the organism with respect to the potencies of differentiation and organization particularly.

BIBLIOGRAPHY

Full descriptions of the experiments and full discussion of their significance, of which this paper is a partial summary, together with pertinent literature, may be found in:

HAMMETT, F. S.: Proliferative reaction of skin to sulfhydryl and its biological significance, Protoplasma, 1931, xiii, 331–347.

HAMMETT, F. S., and HAMMETT, D. W.: The influence of sulfhydryl and sulfoxide on differential growth within the regenerating chela of the hermit crab (*Pagurus longicarpus*), Protoplasma, 1932, xvi, 253–286.

HAMMETT, F. S., and HAMMETT, D. W.: The influence of sulfhydryl on the formation of aberrant disorganized overgrowths in the regenerating right chela of the hermit crab (*Pagurus longicarpus*), Protoplasma, 1932, xvii, 321–358.

REIMANN, S. P.: Hyperplastic reaction of skin to sulfhydryl and its significance in neoplasia, Am. Jr. Cancer (supp.), 1931, xv, 2149–2168.

REIMANN, S. P.: Aberrant growths in regenerating claws of hermit crab under influence of sulfhydryl; their relation to neoplasia, Arch. Path., 1933, xv, 675–697.

EDITORIAL

THE SO-CALLED "CIRCULATORY HORMONES"

In the past few years the rôle of the so-called "circulatory hormones" has been an interesting and ever changing one. The first circulatory hormone was described in 1926 by Frey and Kraut.[1] They isolated a substance from urine which, on intravenous injection into dogs, caused a fall in the blood pressure (in the systolic more than in the diastolic) and an increase in the amplitude of the heart contractions. This substance was called "kallikrein," later "padutin." They observed the same active substance in the blood except that it occurred in an inactivated form and had to be especially treated to produce the reactions. After the active substance had been found in the blood, they tested, by intravenous injection, fresh extracts of liver, kidney, and spleen and obtained results similar to those which had occurred with extracts of urine and blood.

In 1929 Frey observed that the fluid evacuated from a large pancreatic cyst contained an enormous amount of the active substance. On further investigation on animals he found that, after total extirpation of the pancreas, the amount of active substance in the urine decreased as much as 80 per cent. He concluded from his experiments that the pancreas was the site of formation of the active substance, that it was stored in various other organs and tissues, and that it was excreted in the urine. Extracts of pancreatic tissue were found to contain considerable amounts of the active substance. Frey used the urine extract kallikrein, or padutin, for his clinical work, however, and injected it intramuscularly rather than intravenously. The physiologic action was believed to produce vasodilatation and, when injected in the rabbit, dilation of capillaries in the ear was observed. Frey felt that this action was not due to the presence of histamine and choline.

Gley and Kisthonos,[2] in 1929, working in France, prepared an insulin-free pancreatic-tissue extract which they injected intravenously into rabbits. They found that it produced a transitory fall in blood pressure, had vasodilator properties, antagonized the action of epinephrine, and that these effects were not due to choline, histamine, or peptones. This extract may be identical with the circulatory hormone of Frey and Kraut. Standardization of the extract was on the basis of hypotensive units per cubic centimeter. A unit was considered to be the amount of extract necessary to produce barely perceptible evidence of a drop in blood pressure on the tracing when the substance was injected into the jugular vein of a rabbit weighing 2 kg. Wolff, Findlay, and Dessin[3] prepared a pancreatic tissue extract after the

[1] Frey, E. K., and Kraut, H.: Über einen von der Niere ausgeschiedenen, die Hertztatgkeit anregenden Stoff, Ztschr. f. phys. Chem., 1926, clvii, 32–61.

[2] Gley, P., and Kisthonos, N.: Récherches sur la substance hypotensive du pancreas, Presse méd., 1929, ii, 1279–1282.

[3] Wolff, J. B., Findlay, D., and Dessin, E.: Treatment of angina pectoris with a tissue vasodilator extract; preliminary report, Ann. Int. Med., 1931, v, 625–642.

method of Gley and Kisthonos, and they corroborated the latters' findings inasmuch as they found that it caused a primary drop in arterial blood pressure when injected intravenously, slowed the heart rate, and antagonized the action of epinephrine.

After intramuscular injection both the padutin of Frey and Kraut and the pancreatic tissue extract were found to give favorable results, particularly in the treatment of cases of angina pectoris. Frey further noted improvement in cases of essential hypertension and in vascular disease, especially in cases in which intermittent claudication was present. He attributed the beneficial results to the vasodilator effects of the extract. Wolff, Findlay, and Dessin used the pancreatic tissue extract among patients with angina pectoris and reported clinical relief in 55 per cent of cases.

Subsequently, Wolff, in collaboration with the Sharpe and Dohme laboratories, made a new, standard, pancreatic tissue extract in which 1 unit would neutralize the pressor effect on anesthetized dogs of 0.001 mg. of epinephrine. His change in the standardization followed the work of Levine, Ernstine, and Jacobson, in which they demonstrated that, by subcutaneous injection of patients suffering from angina pectoris with 1 c.c. of a 1 : 1000 solution of epinephrine, an anginal attack could be induced, whereas no such attack could be produced among normal control subjects. Wolff reasoned that, if epinephrine injected into certain patients subject to angina pectoris would produce an attack, and if a certain vasodilator obtained from the pancreas moderated the action, the favorable results obtained in treatment might be explained by the ability of the tissue extract to neutralize epinephrine. No further standardization of the pancreatic tissue extract has been made.

Up to this time the development of circulatory hormones had been concerned with lowering of the blood pressure, vasodilator properties, and neutralizing the effects of epinephrine. In 1930 J. S. Schwartzmann[4] prepared an extract from skeletal muscle. He assumed that some sort of antispastic substance was at work during the contraction of active, skeletal muscle. The fact was known that anginal pain sometimes disappeared if the patient continued his muscular effort. This extract was called " myoston " and it was standardized on the basis of its adenosin phosphoric acid content, each cubic centimeter containing 2.5 mg. This standardization was interesting in view of the previous work of Drury and Szent-Gyorgi, who studied the effect on the mammalian heart of extracts of heart muscle, brain, kidney, and spleen, and who found a definite and transient effect on the heart. They isolated the substance which they felt was responsible for the reactions, and from its chemical properties they believed it to be adenylic acid or adenosin phosphoric acid. They found also, that adenosin prepared from yeast nucleic acid had an action identical with that of adenylic acid. They intravenously injected into animals both the tissue

[4] SCHWARTZMANN, J. S.: Muscle extract in the treatment of angina pectoris and intermittent claudication, Brit. Med. Jr., 1930, i, 855–856.

adenylic acid and the adenosin, and they observed a lowering of the blood pressure which they thought was due to the slowing of the heart rate and to general arterial dilatation.

In contrast to these observations Nuzum and Elliott reported that, following intravenous injection of guinea pigs with pancreatic tissue or the Frey " hormone," these substances did not cause a transitory, complete heart block, a supposedly specific test for adenylic acid and adenosin. Wolff, however, noted that 250 micromilligrams of adenosin phosphoric acid corresponded in activity to 1 c.c. of pancreatic tissue extract. It is still impossible to say what the common active substance is.

Myoston, on intramuscular injection, gave excellent results in cases of angina pectoris, as reported by J. S. Schwartzmann, and M. S. Schwartzmann treated a few patients with intermittent claudication very successfully. Myoston has also been prepared for oral administration, but its effect is more transient and, at present, adequate dosage would be almost prohibitive in price.

More recently, excellent results have been reported by clinicians of The Mayo Clinic [5, 6] with the use of pancreatic tissue extract, myoston, muscle adenosin phosphoric acid and adenosin, administered intramuscularly to patients with occlusive disease of the peripheral arteries in whom claudication was the major complaint. To evaluate these extracts more accurately, these workers described a standard test for quantitating claudication. Injections of known vasodilating agents were made before the extracts were administered without effecting a significant change in tolerance to exercise. Following intramuscular administration of the extracts, a sharp increase in the amount of exercise was possible, which persisted for days.

Up to this time the beneficial results have been attributed by various workers to the vasodilator action, but later workers have shown that the improvement bore no relationship to dilation, as measured by standard methods. Pancreatic extract and myoston do not cause a rise in skin temperature or an increase in the rate of heat elimination from a limb. It was thought that the action was probably a direct one on the muscle, supplying a deficient substance or neutralizing an accumulated metabolite in the presence of anoxemia of the muscle. Dietrich and Schwiegk have shown that in animals coronary flow is increased by these extracts. Their use in coronary disease may prove beneficial and they may thus in the future have a wide clinical application.

G. R.

[5] Barker, N. W., Brown, G. E., and Roth, G. M.: Effect of pancreatic tissue extract on muscle pain of ischemic origin (intermittent claudication), Trans. Am. Therap. Soc., 1933, xxiii, 115–119.

[6] Roth, G. M., and Barker, N. W.: Observations on the use of skeletal muscle extract in treatment of intermittent claudication, Proc. Staff Meet., Mayo Clinic, 1934, ix, 390–392.

REVIEWS

Diseases Peculiar to Civilized Man. By GEORGE CRILE, M.D. xi + 427 pages; 15 x 32 cm. The Macmillan Company, New York. 1934. Price, $5.00.

This book is an exposition of the theory of its author that hyperthyroidism, neurocirculatory asthenia, peptic ulcer, and possibly other diseases, are due primarily to the stress and strain of civilization. He calls them "kinetic diseases," and believes them due to an abnormally high sustained activity of the adrenal-sympathetic-thyroid system, or of some of its component parts. Several persons have contributed sections on specialized topics. A section of the book is devoted to a description of certain surgical methods, particularly denervation of the adrenal, and operative procedures upon the sympathetic. Over one-half of the book is given over to detailed case histories. There is a fair bibliography.

This work gives a very readable account of an interesting and superficially plausible theory. The claims made as to the beneficial effects of adrenal denervation are certainly broad. An effort is made to include diabetes in the list of kinetic disorders, and the author makes the flat statement (page 155) that "in a small group of cases, adrenal denervation has abated or cured diabetes." He also believes that the same procedure "abates or cures peptic ulcer." He seems to have established, to his own satisfaction, that bilateral denervation of the adrenals does not cause chronic adrenal insufficiency in man. As he states, the recuperative power of the adrenals is very great.

The accounts of the cases of acute adrenal insufficiency following denervation are of great interest, especially Case 1, page 124. It seems probable that this constitutes an instance of the true experimental production of Addison's disease. Following bilateral denervation of the adrenals, the patient ran a six weeks' course with asthenia, increasing pigmentation, hypotension, and increased concentration of blood non-protein nitrogen (urea). Autopsy indicated degeneration of both adrenals, which was considered secondary to thrombosis and obliteration of the blood vessels.

It seems unnecessary to dwell, in view of the present state of our knowledge, upon the potential dangers which certainly attend any surgical interference with the adrenal glands; and in hands lacking the technical skill of the author of this book, such dangers will doubtless be very much increased.

G. H.

A Textbook of Medicine. By 141 American authors; Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., and FOSTER KENNEDY, M.D., F.R.S.E. Third Edition. xix + 1664 pages; 18 x 25 cm. W. B. Saunders Company, Philadelphia. 1933. Price, $9.00.

In his preface to this work, the Editor states: "In order that physicians and students might have the benefit of an authoritative and up-to-date treatise on every medical subject, it seemed desirable to prepare a textbook of medicine in which each disease, or group of diseases, would be discussed by a writer particularly interested in that subject. This book represents an effort to carry out such a plan." The appearance of the third edition, six years after the first, indicates that the plan has been very successful, and examination of the book reveals the causes of its popularity.

One hundred and thirty well known writers have contributed articles. Though one feels at times that there may have been too much division of labor, the description

of different phases of a subject by various writers is usually managed with coherence in plan and similarity in style of presentation. Thus the section on tuberculosis is divided into seven parts and contributed by five authors. Uniformity in style and quality of their work, however, makes this section a very well organized unit. Certainly in the section on diseases of the kidney, the articles on anomalies of urinary secretion, uremia, and nephritis, would be much better correlated if they were contributed by one author instead of by three, as differences in terminology used may be somewhat confusing to students. This difficulty has been partially obviated by including, in the article on nephritis, Christian's recently published table indicating the terminology of no less than ten different classifications of Bright's disease in common use. This should help the student to a better understanding of this frequently confusing subject.

Any attempt to list even a few of the contributors would be useless, as it would simply consist in calling the roll of many of the most prominent American teachers, all of whom are eminently qualified to discuss the presented subjects.

Generally, the minor criticisms that might be offered are greatly outweighed by the evident good qualities of the book. The articles are uniformly well written, clear, interesting, up-to-date, and with few exceptions, unusually well correlated.

The size and broad scope of the volume make it impossible to review any more detailed account of its contents. Certainly, it may be recommended to students as a modern and complete textbook.

T. N. C.

Clio Medica. Medicine in Persia. By CYRIL ELGOOD, M.D. 105 pages; 11 x 17 cm. Paul B. Hoeber, Inc., New York City. 1934. Price, $1.50.

By this time this series of handy little volumes on medical history ought to be pretty well known to the profession. Everyone interested in medicine in any of its aspects should own these books which can be put in the pocket and read while waiting for any reason, and it is an unusual doctor who does not have spare minutes which are usually wasted. The author of this latest addition was at one time physician to the British Legation in Teheran and had ample time to study the history of one of the most interesting countries on the globe. The land of Scheherezade and Omar Khayyam, of Rhazes and Avicenna, Ismail and Haly Abbas, where 'Jamshid gloried and drank deep,' has a fascinating history beginning indeed with that legendary hero, for as Firdausi puts it:

> Jamshid thus spent
> Another fifty years and did much good.
> He introduced the scents that men enjoy,
> As camphor, genuine musk, gum Banjamin,
> Sweet aloe, ambergris, and bright rose-water.
> Next leechcraft and the healing of the sick,
> The means of health, the cause of maladies,
> Were secrets opened by Jamshid.

Health and disease in early Persia were gifts of the gods and the demons but it seems that the inhabitants did not let it go entirely at that for in the "Shah Nameh" there is the record of an early Caesarian section and the use of an anesthetic which Elgood quotes as follows:

> His birth could not be natural;
> So willeth He who giveth good. Bring thou
> A blue-steel dagger, seek a cunning man;
> Bemuse the lady first with wine to ease

Her pain and fear; then let him ply his craft
And take the lion from its lair by piercing
Her waist while all unconscious. Then imbruing
Her side in blood, stitch up the gash.
Put trouble, fear, and care aside, and bruise
With milk and musk a herb that I will show thee,
And dry them in the shade. Dress and anoint
Rudaba's wound, and watch her come to life.

When Alexander the Great (whose medical history has recently been written by an Italian) went to Persia, Firdausi relates, that an Indian rajah gave him four gifts: a girl, a philosopher, a magic cup and a physician.

A youthful leech who diagnoseth
Disease by making an uroscopy;
So long as he is at the court, the Shah
Will never ail.

We go through the Seleucid and Sassanid ages, the Caliphate and Baghdad school, with Rhazes and Avicenna and Ismail, the great medical trinity of the day, if we may speak of a couple of centuries as a day. The later history is not so brilliant; the Caliphate decayed and the Mongol and Safadid dynasties ruled, then the Qajar dynasty lasted until 1926, when Reza Khan became ruler starting the Pahlevi dynasty. A fascinating story condensed in scarcely more than a hundred pages.

J. R.

L'Exploration Clinique Médicale-Technique et Séméiologie. Published under the direction of ÉMILE SERGENT, Professor of the Faculty of Medicine of Paris. Sections by him and nine collaborators. Paper, two volumes, 1165 pages. Masson and Company, Paris. 1934. Price, 120 francs.

In 1913 Sergent published the first edition of his Traité Élémentaire d'Exploration Clinique Médicale. Five editions followed quickly, with translations into Italian, Spanish and Roumanian. The treatise was both a guide to the student and a stimulus to the teacher. Now after a lapse of years Sergent brings up to date the newer knowledge of the technic of medical examination and the signs of disease.

The two volumes comprise sections on: The Respiratory Apparatus, by Émile Sergent; The Circulatory Apparatus, by Camille Lian; The Nervous System, by Paul George; The Sympathetic Nervous System, by René Mignot; Radioscopie and Radiography of the Thorax, by Pierre Pruvost; Radiography of the Nervous System, by Pruvost; Examination of the Abdomen, by R. d'Heucqueville; Examination of the Digestive Tract, by d'Heucqueville; Laboratory Methods Applicable to Diseases of the Digestive Tract, by Pierre Oury; Examination of the Spleen, by d'Heucqueville; The Liver and Hepatic Function, by Ribadeau-Dumas; The Pancreas, by Bordet; Kidneys and Urinary Function, by Ribadeau-Dumas; Analysis of Urine, by Rene Hazard; Examination of the Blood, by Pruvost and Bordet; Elementary Laboratory Methods, by Pruvost; Radiology of the Abdomen, Extremities and Vertebral Column, by Pruvost.

The volumes are well printed, with numerous excellent plates and illustrations. There is a good index. This new edition of a very popular earlier work will no doubt serve the same useful purpose as its predecessor and will meet with approval. It has been edited with much care and gives due credit to work done outside of France.

W. B. S.

The Science of Radiology. Edited by OTTO GLASSER, Ph.D., of the Cleveland Clinic Foundation. xiii + 450 pages; 17.5 x 25 cm. Charles C. Thomas, Springfield. 1933. Price, $4.50.

This is a much needed and timely book, sponsored by the First American Congress of Radiology. The editor, Otto Glasser, is well qualified by virtue of his extensive experience in Europe and America in the physics of radiology, and also through his close contact with its clinical applications. The contributors are all outstanding men, occupying high positions as physicists or clinicians.

The book depicts "the outstanding features developed in the science of radiology from the time of Roentgen's discovery, to the period of this congress" (First American Congress of Radiology). The various chapters are written by men particularly adapted to the given phase they treat. The space is well allocated to the various aspects of radiology, including history, physics and all branches of medicine affected. The correlation of x-ray and radium therapy which are inseparable in clinical application, is well brought out,—a valuable feature in a treatise of this character. The full bibliography adds value to the book as a work of reference. It is so interestingly written that it reads almost like fiction, yet it includes a vast amount of information.

G. E. W.

The Doctor and Citizenship. By THURMAN D. KITCHIN. 89 pages; 14 × 20.5 cm. Christopher Publishing House, Boston. 1934. Price, $1.50.

Dr. Kitchin practiced medicine for some years and then was made Dean of the Medical School of Wake Forest College and more recently he was chosen as president of the College. His book consists of ten articles, partly addresses and partly essays, mostly about medicine and citizenship and kindred topics. He stresses the fact that to be a good doctor the physician must be a good citizen as well. It may best be described by quoting one of the running heads of the accompanying advertising leaflet, "An inspiring book of medical culture." That tells the story.

J. R.

The Medical Profession and the Public. (A collection of ten papers.) 112 pages. American Academy of Political and Social Science, Philadelphia. 1934. Price, $1.00.

This symposium, presented at a joint meeting of the College of Physicians of Philadelphia and the American Academy of Political and Social Science in Philadelphia, February 7, 1934, discusses the whole subject of the physician's relation to the public. The problem from the physician's standpoint is discussed by Drs. Nathan B. Van Etten, Henry E. Sigerist, Grant Fleming, Roger I. Lee, Morris Fishbein, and Thomas Parran, Jr. The sociological side of the question was discussed by the following: Messrs. James H. S. Bossard, Edgar Sydenstricker, Michael M. Davis and William T. Foster.

Throughout the symposium the reader will find a good many stimulating comments, many of which he may not agree with. The first speaker emphasizes the trend toward socialized medicine. While in general this is the stand taken by the lay speakers, the physicians on the program took a position against it. The last speaker emphasizes: "What the public does demand is the right to say, not how medicine shall be practiced, but how it shall be purchased and paid for; and who has a better right than those who do the paying? In any event, it is folly to burden physicians any longer with business affairs which they have notoriously mismanaged, and for which they are not trained, in which they are not interested, and which interfere with that single-hearted devotion to patients which is the glory of their profession."

Fishbein, as the last speaker for the medical profession, states: "It is conceivable that out of many of the experiments that have been made and are being made, out of the scientific advancement of medicine itself, there may be a greater and greater tendency toward discounting individuality in medical care. . . . The medical profession feels that the sick man is still an individual, a human being. . . . It has shown repeatedly its willingness to work with economists, sociologists and statesmen toward schemes for making such individual medical care feasible for the vast majority of our people."

J. L. McC.

COLLEGE NEWS NOTES

Acknowledgment of the following gifts to the College Library of publications by members is herewith made:

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa—one reprint;
Dr. John M. Dyson (Associate), Hazelton, Pa.—one reprint;
Dr. Dunne W. Kirby (Associate), Philadelphia, Pa.—6 reprints;
Dr. Samuel A. Shelburne (Associate), Dallas, Texas—5 reprints.

Dr. Warfield T. Longcope (Fellow), Baltimore, Md., has been elected a member of the board of scientific directors of the Rockefeller Institute for Medical Research, succeeding the late Dr. William H. Welch.

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa, Dr. Benjamin H. Orndoff (Fellow), Chicago, Ill., and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., are among the distinguished guest speakers on the program of the Omaha Mid-West Clinical Society at its annual assembly in Omaha, October 29 to November 2.

At the tenth annual meeting of the American Association of the History of Medicine, held some months ago in Cleveland, the following Fellows of the College were elected as indicated:

Dr. E. B. Krumbhaar, Philadelphia, Pa., *President,*
Dr. W. S. Middleton, Madison, Wis., *Vice-President,*
Dr. E. J. G. Beardsley, Philadelphia, Pa., *Secretary-Treasurer,*
Dr. Carl V. Weller, Ann Arbor, Mich., *Member of the Council.*

Dr. J. Gurney Taylor (Fellow), Milwaukee, Wis., has been appointed Chairman of the newly organized subsidiary board for Part III of the National Board of Medical Examiners.

Dr. Virgil H. Cornell (Fellow), Curator of the Army Medical Museum, has been reëlected Secretary of the National Institute of Health for the coming year.

Dr. S. A. Slater (Fellow), Worthington, Minn., has been elected President of the Southern Minnesota Medical Association for the forthcoming year. Dr. Charles W. Mayo, Rochester, Minn., was elected First Vice-President, Dr. J. C. Michael, Minneapolis, Minn., Second Vice-President, and Dr. H. C. Habein (Fellow), Rochester, Minn., Secretary.

Dr. Burton R. Corbus (Fellow), Grand Rapids, Mich., became Acting Secretary of the Michigan State Medical Society on September 1, 1934.

Dr. Virgil P. Sydenstricker (Fellow), Augusta, Ga., gave the lecture on the "Treatment of the Anemias" in connection with the series of lectures at Sandersville, Ga., sponsored during the past summer by Emory University and University of Georgia under the supervision of the State Board of Health.

Dr. Wallace M. Yater (Fellow), Washington, D. C., has been elected Vice-President of the Washington Heart Association.

Drs. Arthur C. Christie (Fellow), J. Russell Verbrycke, Jr. (Fellow), Thomas A. Groover (Fellow), and Henry C. Macatee (Fellow) are among those who will serve upon the District of Columbia Health and Hospital Council, composed of representatives of the medical, dental and civic societies, as recently organized under the sponsorship of the Council of Social Agencies. Ross Garrett, Health Secretary of the Council of Social Agencies, has announced that this newly organized Health and Hospital Council "will be available to all government authority as a medium of ascertaining opinion and reaction of the majority in professional, administrative and lay organizations representing the citizens in the district."

Dr. Joseph A. Mendelson (Associate) has been retired from active service as Major, Medical Corps, U. S. Army, Station Hospital, Fort F. E. Warren, Cheyenne, Wyo., because of physical disability. He has planned to return to Tientsin, China, to engage in the practice of Internal Medicine.

Dr. Henry I. Klopp (Fellow), Superintendent and Physician in Chief of the Allentown (Pa.) State Hospital, became a Life Member of the American College of Physicians on August 20, 1934.

Dr. Edward Schons (Fellow), St. Paul, Minn., retiring President of the Minnesota Radiological Society, addressed the joint meeting of the Minnesota Radiological Society and the Minnesota State Medical Association at Duluth, July 16, 1934, on "The Value of Cholecystography by the Oral Route, with an Analysis of 189 Operated Cases."

On September 1, 1934, Dr. H. Beckett Lang, heretofore Director of Clinical Psychiatry at the Marcy State Hospital, Marcy, N. Y., became Director of Clinical Psychiatry at the Pilgrim State Hospital, Brentwood, Long Island.

Dr. Daniel F. Milam (Fellow), has been transferred to Panama by the International Health Board of the Rockefeller Foundation.

Dr. James L. McCartney (Fellow), who for the past three years has been Psychiatrist and Director of Classification under the New York State Department of Correction at the Elmira Reformatory, resigned from that position September 1, to enter the private practice of neuropsychiatry in Portland, Oregon. Under a grant from the New York Academy of Medicine, Dr. McCartney has written a book on the classification of prisoners which is now in press.

A Plan to Evaluate Independently Serologic Procedure for the Diagnosis of Syphilis in the United States

Since the serologic conferences at Copenhagen and Montevideo, there has been an increased interest in the relative value of serologic tests for the diagnosis of syphilis. At these conferences the test of only one serologist of the United States was presented for consideration. There are a number of excellent serologists in this country, many of whom have described original modifications of the complement-fixation and precipitation tests for syphilis. It is felt that the tests of these workers merit consideration.

The United States Public Health Service is coöperating with the American Society of Clinical Pathologists in the drafting of a plan to evaluate independently serologic procedure for the diagnosis of syphilis in this country. Briefly, the plan contemplates the collection of specimens of blood from at least 1,000 individuals and the distribution of comparable specimens to the laboratories of serologists who have described an original modification of a complement-fixation or precipitation test for the diagnosis of syphilis. The donors of the specimens will be carefully selected so as to measure both the specificity and sensitivity of the serologic procedure. The sending of specimens to workers at considerable distance from the point of collection will be expedited by the use of the most modern transportation facilities, while the delivery of specimens to nearby serologists will be delayed so as to make the delivery time approximate that for those workers at the more remote points.

A committee of five members consisting of two specialists in the field of clinical syphilology, two members of the American Society of Clinical Pathologists, and one officer of the United States Public Health Service will organize the plan of study and, after all laboratory reports have been submitted by participating serologists, will interpret the results on the basis of clinical findings. The collection of the specimens will begin about December 1, 1934, and a number of serologists will be invited to take part in the evaluation scheme.

It is possible that the name of some serologist who has described an original modification of a test for syphilis may have been inadvertently omitted. Any serologist desiring to participate will be extended an invitation upon presentation of suitable proof as to the originality of his modification of a serologic test. A brief description of the plan will also be sent to those workers who may be interested.

Correspondence should be addressed to the Surgeon General, United States Public Health Service, Washington, D. C.

OBITUARY

DR. JAMES LESTER JUNK

Dr. James Lester Junk, of Connellsville, Pa., died May 20, 1934, as the result of a ruptured abdominal aneurysm, after an illness of but a few days. He was 54 years of age, having been born October 3, 1879, at the Junk homestead at Laurel Hill, in Fayette County. After attending grade school, he first entered California State Teacher's College, and, later, Pennsylvania State College. It was at State College that his proficiency at football first began to attract the wide attention which, later, at the University of Pennsylvania, where he studied medicine, won him the signal honor of a place on Walter Camps All-American team of 1905.

Dr. Junk graduated from the Medical School of the University of Pennsylvania in 1907, with highest honors, and after serving in a Philadelphia hospital and finishing a postgraduate course at Harvard Medical School, began the practice of his profession at Dunbar, Pa., in 1908, removing after four years to Connellsville.

During the war he held a commission as first lieutenant, and was in charge of the base military hospital at Aberdeen, Maryland. Later he joined the National Guard, and was appointed Major in the Medical Corps in 1922, which rank he held until his death.

Always deeply interested in children and their education, he served for years on the Connellsville Board of Education, holding the office of President for five consecutive years. In 1909 Dr. Junk married Miss Janet Handlin, of Dunbar, Pa. Mrs. Junk died in 1914. Dr. Junk is survived by his mother and four brothers.

He was a past president of the Fayette County Medical Society, and was also a member of the Pennsylvania State Society, of the American Medical Association, and had been an Associate of the American College of Physicians since December 30, 1921. He belonged to the Sigma Alpha Epsilon fraternity and was a Mason.

So high a place did Dr. Junk occupy in the regard of his community, both as citizen and physician, that all united to show him honor. His body lay in state in the State Armory, and every medical, fraternal, educational and civic group of that section took action to pay their final respects. Many of the stores of the city closed during the services—all attesting to the deep regard and appreciation in which he was held, and to the sorrow felt at the ending of a life so full of usefulness and devotion to others.

E. Bosworth McCready, M.D., F.A.C.P.,

Governor for Western Pennsylvania.